Evidence Report:

Risk of Altered Sensorimotor/Vestibular Function Impacting Critical Mission Tasks

Human Research Program

Human Health Countermeasures Element

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I. PRD RISK TITLE: RISK OF ALTERED SENSORIMOTOR/VESTIBULAR FUNCTION IMPACTING CRITICAL MISSION TASKS

Description: Given that altered gravity transitions lead to changes in sensorimotor/vestibular function that manifest in motion sickness, spatial disorientation, decrements in postural control and locomotion, and fine motor control deficits, there is a possibility that crew will experience performance decrements in manual/vehicle control, extravehicular activities, and egress during and following these transitions.

II. STATUS

- *Active*: Work/research is currently being done towards this risk

III. EXECUTIVE SUMMARY

Long duration spaceflight alters sensorimotor/vestibular function which manifests as motion sickness and decrements in spatial orientation, postural control and locomotion, and manual and fine motor control. The risk of impairment is greatest during and soon after G-transitions when performance decrements may have high operational impacts (manual landings, immediate egress following landing, early extravehicular activities (EVAs). There is a large inter-subject variability in the level of symptoms and time course of recovery. The possible alterations in sensorimotor performance are of interest for lunar and Mars missions due to the prolonged microgravity exposure during transit followed by landing tasks in a novel environment.

There have been numerous human scientific investigations to date conducted during spaceflight, after landing, and in spaceflight analogs. Recent studies have specifically improved the risk characterization of changes in perception, motion sickness, neuroimaging, postural and locomotion control, manual control, and fine-motor coordination. However, given the difficulty in obtaining measurements during and soon after G-state transitions, evidence for initial decrements immediately following G-state transitions remains limited. In addition, computer-based models and animal spaceflight studies have helped us simulate and/or predict the impacts of physiological adaptations on operational performance and have improved our understanding of the underlying physiological mechanisms. The most significant gaps in characterizing the risk include manual control ability around G-transitions, incidence and severity of motion sickness during water landings, time course of vestibular adaptations during and following varying mission lengths for which we have limited data, ability to perform egress/EVAs soon after G-transition, and the effects of partial gravity.

Current and future studies on countermeasures are generally focused on pharmaceutical and/or non-pharmaceutical mitigation of sensorimotor decrements as well as a variety of preflight, inflight and postflight training/rehabilitation approaches. While these countermeasures have been traditionally focused on specific outcomes, e.g., motion sickness, specific operational tasks, manual control or egress, there is an acknowledgement that future countermeasure work will need to be more integrated across tasks and multi-disciplinary where feasible. Integrating multiple modalities or countermeasures may be necessary to optimize the efficiency of risk mitigation. For example, artificial gravity (centrifuge) would likely prevent multisensory integration changes and mitigate most of this risk, but an implementable design does not currently exist. Exploration countermeasures will also need to be implemented autonomously with the ability to self-administer, preferably based on objective monitoring of an individual’s function and performance. Additional work on models of adaptation and sensorimotor standards should improve vehicle design requirements, exploration mission timeline planning, implementation of specific countermeasures, and go/no-go decision-making guidelines regarding in-mission operational tasks.

Finally, while much of the focus over the past half-century has been on the risks to operational performance, long term monitoring is needed to characterize the long-term health effects of this risk. As more humans travel further and longer in space, and the commercialization of space involves a greater diversity of participants, this information will be vital to ensure that diagnoses and treatments are available, specific to future astronaut populations.

IV. INTRODUCTION

Control of vehicles and other complex systems is a high-level integrative function of the central nervous system (CNS). It requires well-functioning subsystem performance, including good visual acuity, eye-hand coordination, spatial and geographic orientation perception, and cognitive function. Evidence from spaceflight research demonstrates that the function of each of these subsystems can be altered by reducing gravity, a fundamental orientation reference, which is sensed by vestibular, proprioceptive, and haptic receptors and used by the CNS for spatial orientation, posture, navigation, and coordination of movements. The available evidence also illustrates that both individual- and mission-related factors, e.g., duration, influence the severity of the decrements and the time course of adaptation to the new G-state.

There is only limited operational evidence that these alterations cause functional impacts on mission-critical vehicle (or complex system) control capabilities. Furthermore, while much of the operational performance data collected during spaceflight has not been available for independent analysis, those that have been reviewed are somewhat equivocal owing to uncontrolled (and/or unmeasured) environmental and/or engineering factors. Whether this can be improved by further analysis of previously inaccessible operational data or by development of new operational research protocols remains to be seen. The true operational risks will be estimable only after we have filled the knowledge gaps and when we can accurately assess integrated performance in off-nominal operational settings (Paloski et al. 2008).

Thus, our current understanding of the Risk of Altered Sensorimotor/Vestibular Function Impacting Critical Mission Tasks is limited primarily to extrapolation of scientific research findings. Since there are limited ground-based analogs of the sensorimotor and vestibular changes associated with spaceflight, observation of their functional impacts is primarily limited to studies performed in the spaceflight environment. Fortunately, many sensorimotor and vestibular experiments have been performed during and/or after spaceflight missions since 1959 (Reschke et al. 2007a). While not all of these experiments were directly relevant to the question of vehicle/complex system control, most provide insight into changes in aspects of sensorimotor control that might bear on the physiological subsystems underlying this high-level integrated function.

V. EVIDENCE

A. Spaceflight Evidence

1. Evidence from Spaceflight Operations

An accurate assessment of the risks posed by the impacts of physiological and psychological adaptations to spaceflight on control of vehicles and other complex systems must account for the potentially offsetting influences of training/recency and engineering aids to task performance. Thus, it behooves us to review performance data obtained from spaceflight crews engaged in true mission operations. Evidence of operational performance decrements during spaceflight missions has been obtained from several sources; however, to our knowledge no well-designed scientific studies have been performed on critical operational task performance, so interpretation is frequently confounded by small numbers of observations, inconsistent data collection techniques, and/or uncontrolled engineering and environmental factors. Much of the relevant, extant operational data has been previously inaccessible to (or uninterpretable by) life sciences researchers. Recent programmatic changes have putatively improved access to both data and experts to help with interpretation.

a. **Crew Verbal Reports**

A number of crew verbal reports were obtained early after flight by the authors of this review (Reschke and Clément 2018). While difficult to combine, owing at least in part to the lack of standardized questions and structured interview techniques, these reports are informative in that they provide insight into the individual crewmember perceptions. As an example, the following transcript obtained by Dr. Reschke captures impressions from a Shuttle commander obtained immediately (< 4 hours) after flight. The first part of the discussion focused on target acquisition tasks the commander performed for Dr. Reschke during the flight and his difficulties with nausea, disorientation, posture, locomotion, etc. after the flight (*italicized text* indicates the crewmember's responses to the Dr. Reschke's questions).

Did you try to limit your head movements? *Oh yes, definitely.* When you were trying to acquire the targets only...did you notice any difficulty in spotting the targets? *Oh yeah, oh yeah.* Did it seem as though the target was moving or was it you? *I felt that it was me. I just couldn't get my head to stop when I wanted it to.* So it was a head control problem? *Yeah, yeah in addition to the discomfort problem it caused.* So when you first got out of your seat today, can you describe what that felt like? *Oh gosh, I felt so heavy, and, uh, if I even got slightly off axis, you know leaned to the right or to the left like this, I felt like everything was starting to tumble.* When you came down the stairs did you feel unstable? *Oh yeah, I had somebody hold onto my arm.* Did you feel like your legs had muscle weakness, or … was it mainly in your head? *It was mainly in my head.*

Every crewmember interviewed by one of us on landing day (>200 crewmembers to date) has reported some degree of disorientation/perceptual illusion, often accompanied by nausea (or other symptoms of motion sickness), and frequently accompanied by malcoordination, particularly during locomotion. Of particular relevance to the ability to perform landing tasks, common tilt-translation illusions (see below) include an overestimation of tilt magnitude or misperception of the type of motion. Most also reported having experienced similar symptoms early in flight. However, except in the most severely affected, there seems to be no correlation between the severity of the symptoms following ascent and those following descent. The severity and persistence of post-flight symptoms varies widely among crewmembers and increase with mission duration. Symptoms generally subsided within hours to days following 1-2 week Shuttle missions but persisted for a week or more following 3-6 month Mir Station and International Space Station (ISS) missions.

The degree to which these psychophysical effects might affect piloting skills is difficult to judge, as recent (relative to launch), intensive training may have offset any impact on Shuttle landings, especially under nominal engineering and environmental conditions. Long duration Mir and ISS crewmembers to date have only piloted ballistic entry spacecraft, which parachute in, allowing no human control inputs during the last 15 minutes before landing.

The following crew reports focus on the perceived ability of the crewmembers to egress the Shuttle immediately after landing in case they could not be assisted by the ground team due to an emergency. The responses represent the individual variability. The crewmembers' response to the question: "***Could you have performed an emergency egress at wheels stop?"*** are shown in italic**.** (note PLT=pilot, MS=mission specialist, CMD=commander, PS=payload specialist)

PLT *Yes. I don't really know how the disorientation would have affected me...coming down the ladder and getting out of the front seat there's a lot of turning. I think if I would have gone slow, I could have done it.*

PLT *No. It would have been difficult. I could have gotten out, but not in any hurry. No way. [**What if you had to go out from the top**?] I don't know if I could have made it. I could try.*

MS *Yes.*

PLT *Yes. It's a very personal thing. If I moved slowly and deliberately, I could have gotten out. The fast motions cause you to crash over.*

PLT *I'm not sure. It would have been a real workout. We had our strength, and we would have banged around, and we would have been slower, but it's a continuum, not yes or no, it depends. **[What about though the hatch on top?]** I think so, it would have been a real chore. Very, very demanding. Somebody ought to try it. And sooner than 40 minutes.*

MS *No. Post-landing emergency egress is questionable. If you've got to get out in a hurry-- know I would have trouble. I tried to stand up, and immediately sat back down again. As I stood up, the lockers translated down, it didn't feel right. If I had to get out of the Orbiter during the first 5 or 10 minutes it would have been tough. It wouldn't have been pretty. If I had to do anything that required any real coordination... **[What aboutthrough the hatchon top?]** Very difficult. No way. People are fooling themselves, the whole business of throwing a rope out and lowering down the side--no way. Some guys jump up and are ready to go. Some people more readily adapt.*

MS *Yes.*

PS *No. I was unsteady, had ataxic gait, couldn't correct for my mistakes.*

CMD *No. I think we would have major problems. **[What aboutcomingout of the top?]** Impossible.*

MS *No. I think there would be a pile of people in the hatch or at the bottom of the hatch. Vestibularly, it would worry me. Getting to the slide, I would have fallen at least once.*

MS *Yes or No. I think if your life is threatened, you could run, but you're going to fall doing it. It would be one of these that you're going to get up and fall and get up and run. Sure, when there's a fire behind you, you're going to find your balance pretty fast. **[What about going down the slide?]** You would go flat on your face.*

CMD *No. The pilot and commander would have a real problem getting out of their seat. We don't have anything to stand on. Can't stand up straight. Looked for help from Life Sciences--might be good to have something to pull myself out. The pilot and commander would have a hell of a time if it was life essential to get out.*

PS *Yes or No. Depends on where you'd have to exit--out the hatch, ok. Out the top, it would be hard. Have to go slower.*

CMD *Yes. It would have been slow, would not have been pretty. I would have tumbled down the chute, but I could have gotten out.* ***[What about going down the slide?]*** *It would have been tough, because of the suit.*

PLT *Yes. Yeah, Yeah, Yeah I could have gotten out.* ***[What about going down the slide?]*** *Yeah.*

MS *Yes. Yeah, hard to say, because if you were in an emergency, the adrenaline rush just sort of takes over. And it wasn't until I stopped being dizzy that I noticed I was really nauseated. So you tend to think, when you get done what you need to do and then your body has time to betray you.*

MS *Yes or No. Probably couldn't have run, but I could have walked. Getting the slide out was my job. I could have done it not fast, but slow and methodically.*

b. Shuttle Entry and Landing Spatial Disorientation

Despite intensive training for all Shuttle commanders and pilots, some Shuttle landings were outside of the desired performance specifications, perhaps, in part, because of spatial disorientation. Shuttle entry and landing spatial disorientation (SD) differs from aviation SD, at least in terms of prevalence. Most instrument rated aircraft pilots have experienced SD, but episodes occur relatively infrequently in ordinary flying. In contrast, stimuli capable of producing SD were present during every Shuttle landing. At issue is whether the astronaut commander could successfully fly through the SD. Tilt-translation illusions and other sensorimotor disturbances (see below) did not occur in astronauts practicing approaches in the Shuttle Training Aircraft (STA), so their first actual experiences with these illusions occurred during their first actual return from space. Crews were forewarned about them, but they did not know how to predict the direction and magnitude of the effect, so a first-time flier did not know in advance which way to compensate. This was generally handled operationally by requiring commanders to have previous spaceflight experience (as pilots). Fortunately, for all Shuttle flights flown, there were no accidents specifically attributed to SD. However, several lines of circumstantial evidence suggest that the margin for error may have been less than generally recognized.

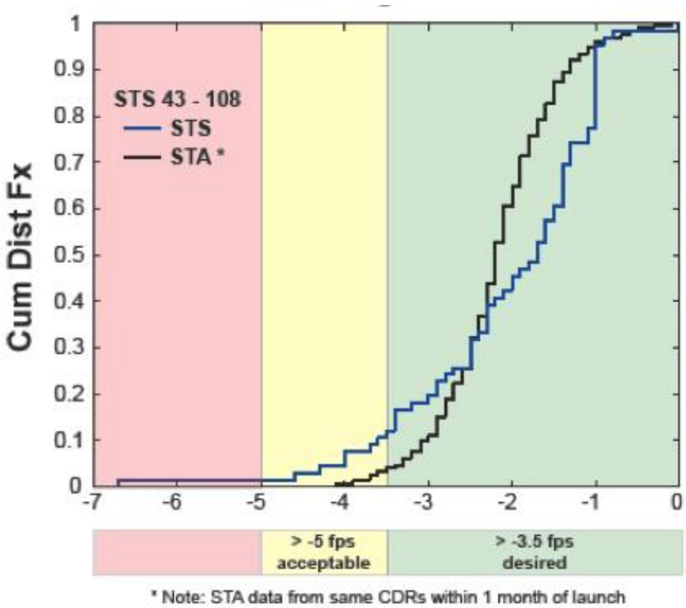


Figure 1 STS versus STA landing performance

Cumulative distribution functions allowing comparison between landing performances (vertical velocity at touchdown) before flight in the Shuttle Training Aircraft (STA) and those at the end of mission in the Space Shuttle (STS).

Evaluation of Shuttle landings suggested that performances during orbiter landings were more variable compared to the preflight Shuttle Training Aircraft landings. Key landing parameters such as sink rate and touchdown speed exceeded desired limits across several missions (Figure 1). Data mining of the first 108 Shuttle landings showed 20% exceeded touchdown speeds and 12% exceeded touchdown sink rates (Clark et al. 2019; Moore et al. 2008). Preliminary data mining of the postflight neurological exams suggested impaired dynamic equilibrium was associated with Shuttle landings that were shorter, faster, and harder (McCluskey et al. 2001).

The "Portable In-flight Landing Operations Trainer" (PILOT) was a laptop computer simulator that was flown as a tool for helping the mission commander and pilot maintain their proficiency for approach and landing during longer duration Space Shuttle flights (Kennedy et al. 1997; Life Science Data Archive 2020). One Shuttle commander who experienced vertigo during the landing (personal communication) attributed the “just-in-time” training of the PILOT to be able to lower perceived cognitive workload and effectively pilot through spatial disorientation to complete a successful landing. Another who did not experience SD described how performance on the PILOT increased awareness of the need to compensate for the tendency to lag the desired flight path. The PILOT was an important tool to maintain task proficiency during the longer missions that approached 18 days.

c. Apollo Lunar Landing Spatial Disorientation

The Apollo Lunar Module (LM) had a digital autopilot that on later missions was capable of fully automatic landings. While the Apollo crews used the autopilot through most of the descent, all elected to fly the landing phase manually, using angular rate and linear velocity control sticks to adjust the vehicle trajectory while visually selecting the landing point. Landing sites and times were chosen so that the sun angle provided good visibility, but the crews had problems recognizing landmarks and estimating distances because of ambiguities in the size of terrain features. The vehicles had no electronic map or landing profile displays. The commander flew visually, designating the landing spot using a window reticle, while the second astronaut verbally annunciated vehicle states and status. Unfortunately, the landing area was generally not visible to the crew until the LM pitched to nearly upright at an altitude of about 7000 feet and distance of about 5 miles from touchdown with only 1-2 minutes of fuel remaining. Visibility was reduced by the window design (views downward and to the right were blocked) and lunar dust blowback also impaired surface and attitude visibility. For example, the Apollo 11 and 12 crews reported difficulty in nulling horizontal rates during landing because of blowing dust, and the Apollo 12 and 15 crews reported virtually no outside visibility in the final moments of landing. Visibility was improved in later missions by new hovering maneuvering procedures that reduced blowing dust.

Horizontal linear accelerations could not be avoided during the gradual descent to the landing zone or during hover maneuvers just before touchdown. Since lunar gravity is only 1/6 that on Earth, lunar landers had to pitch or roll through angles six times larger than on Earth to achieve a given horizontal acceleration using the engine thrust vector. The directional changes in gravito-inertial force these tilts created would have been larger than those on Earth, arguably making tilt-translation ambiguity illusions more likely. The Apollo crews trained for their missions in a 1/6 g Lunar Landing Training Vehicle, which did not simulate the vestibular effects of 1/6 g. Prior to their missions the only 1/6 g vestibular stimulation they received was during limited parabolic flight training. The Apollo crews did not acknowledge any spatial disorientation events during landing. They did later admit feeling a little “wobbly” when they emerged to walk onto the lunar surface but reported that coordination improved steadily during first few hours of lunar ambulation.

d. Apollo Landing Geographic Disorientation

The Apollo Lunar Module (LM) utilized inertial navigation, updated by occasional star sights, radar orbital data from Earth, and radar altimetry during descent. Nonetheless, there was uncertainty in the accuracy of their computed position as they descended into the landing zone. Since crews could not look straight down, the final approach trajectory to the landing area had to use low angles (16-25˚) so crew could see ahead. Mission planners only knew the landing zone terrain to 10 m resolution, so the crews had to confirm visually the LM trajectory and then sight the computer’s anticipated touchdown point using a front window reticle.

Given the fractal nature of lunar craters, identification of surface features was challenging. Humans interpret surface shape from shading based on a “light comes from above” assumption. This can create a “Moon crater” illusion (Ramachandran 1988) in which distant concave features, such as lunar craters, can be perceived as convex objects, such as hills, when viewed looking “down sun.” The crews had to choose a suitably flat landing area, as judged by surface albedo and the absence of shadows indicating small craters or fissures. Landings were planned with sun elevations of 5-23˚, so shadows were of moderate length, and with the crew facing down sun at a slight angle, so that shadows would visible. The human eye can resolve 1.5 ft detail at a distance of about 4000 ft. As more surface details became visible, the commander typically redesignated the landing point (often several times), and eventually took over and flew manually, usually to a point somewhat beyond the final computer redesignated spot. He judged horizontal velocity looking out the window or using a cockpit Doppler radar display, and he used the LM shadow as a gauge, while listening to callouts of altitude, altitude rate, horizontal velocities, and fuel status. Since surface slope is impossible to judge visually looking straight down, the commander chose the final landing spot looking horizontally, then flew over it and began final descent.

At 50-100 feet, dust often obscured the outside view, and the vertical descent to touchdown sometimes had to be made relying primarily on instruments. The descent engine was cut off just before touchdown to avoid explosion or damage should it contact the surface. The landing gear design assumed a maximum surface elevation difference of two feet within the landing gear footprint and a maximum 12˚ terrain slope (Rogers 1972). Finding a flat landing spot was highly desirable since vehicle tilts on the surface complicated surface operations and subsequent takeoff.

All six Apollo landings were ultimately successful. However, the Apollo 15 crew experienced geographic disorientation. When they pitched over, they could not identify the craters they were expecting, and the commander had to choose a landing spot in an unplanned area. Maintaining full awareness of the terrain immediately beneath the lander was usually impossible during the final phase of landing, and in one case the LM engine was damaged on touchdown (Jones and Glover 2010; Mindell 2008). The Apollo 12 commander encountered heavy dust blowback and said, "*I couldn't tell what was underneath me. I knew it was a generally good area and I was just going to have to bite the bullet and land, because I couldn't tell whether there was a crater down there or not.*" He later added, "*It turned out there were more craters there than we realized, either because we didn't look before the dust started or because the dust obscured them.*" The following mission, Apollo 14, landed safely, but on a 7° slope. Apollo 15 experienced severe dust blowback that contributed to making the hardest landing of the program (6.8 ft/sec), with the vehicle straddling the rim of a 5 ft deep crater, buckling the bell of the descent engine and causing an 8˚ vehicle tilt. Apollo 16 and 17 experienced less dust obscuration and landed closer to level.

It seems likely that similar problems will be encountered when crews land vehicles on Moon again and on Mars. Improved navigation aids could help to avoid geographic disorientation, and increased reliance on auto-land capabilities could help maintain the landing performance within equipment specifications. However, improved training techniques, including realistic simulation of visual-vestibular inputs, will likely be required should commanders choose to use manual landing modes. The challenge of manual landing is likely to be much greater for Mars landings, owing primarily to the increased transit time in microgravity. A combination of more profound adaptation to microgravity and decreased training recency will likely increase substantially the risks associated with manual landing on Mars. While continuous or intermittent artificial gravity, created by rotating all or part of the vehicle during transit, may mitigate this risk as well as other biomedical risks, the impact of prolonged exposure to a rotating environment on piloting a spacecraft would need to be investigated before committing to such a solution.

e. Rendezvous and Docking

A top priority in the U.S. space program is assuring crew and vehicle safety. This priority gained significant focus in June 1997 following the collision of the Progress 234 resupply ship with the Mir space station during a manual docking practice session. There were two separate attempts to dock the Progress with the Mir that day. In the first attempt, docking was aborted after the radar used for range calculations apparently interfered with a camera view of the Progress. In the second, near fatal attempt, mission managers decided to turn the radar off and leave the camera on. For this arrangement to work the Mir commander asked his two crewmates to look for the Progress approach through a porthole, and once sighted, to provide range information with handheld range instruments. Trouble began when neither the camera view nor the visual spotters could locate the Progress as it closed on the station. When spotters moved between modules to obtain a better view, they lost their frame of reference and were uncertain which direction to look. Once spotted, the Progress's speed was above an acceptable rate, and it was very close to the Mir. Braking rockets on the Progress, fired by the Mir commander, failed to slow the velocity of the approaching spacecraft. No range information or other position data were available to assist the commander. To complicate matters, one of the other crewmembers may have bumped into the commander as he attempted to make last second inputs to the approaching Progress via joystick. The resulting collision tore a portion of the solar panel on the Mir, punched a hole in the Spektr module, and caused a decompression of the station.

Loss of situational awareness, spatial disorientation, and sensorimotor problems, including difficulties with vision, head-hand-eye coordination, and an inability to judge distance and velocity with limited feedback likely contributed to this outcome. Target acquisition studies have shown dramatic changes in the speed at which target visualization can be achieved, delaying response time by as much as a 1000 ms (Kolev and Reschke 2014). Eye-hand response could take as long as another full second. A delay of 2 sec would seriously compromise the operational reserve to decrease velocity when a spacecraft is closing. After the fact, Ellis (2000) performed a rigorous, quantitative analysis of the available visual and non-visual information and suggested a number of potential sensorimotor and cognitive/psychophysical contributions to the crash. To avoid human factors contributions to future crashes, such rigorous analyses should be performed well before attempting any three-dimensional visual-motor control task.

f. Teleoperator Tasks

The International Space Station (ISS) teleoperation system was heavily used during construction, and it has continued to be used to support extravehicular activities (EVA) operations, as well as in grappling/docking of rendezvousing cargo vehicles (Ruttley et al. 2010). Training and operating the Shuttle and ISS telerobotic manipulator systems as well as telerobotically controlled surface rovers presents significant sensorimotor challenges (Currie and Peacock 2001; Lathan and Tracey 2002; Menchaca-Brandan et al. 2007). These systems are usually controlled using separate rotational and translational hand controllers, requiring bimanual coordination skills and the ability to plan trajectories and control the arm in some combination of end-effector or world reference frames. The abilities to visualize and anticipate the three-dimensional position, motion, clearance, and mechanical singularities of the arm and moving base are critical. Thus, operators must have the cognitive abilities to integrate visual spatial information from several different reference frames.

Often the video cameras are not ideally placed, and in some situations (e.g., ISS operations) the views may actually be inverted with respect to one another, so cognitive mental rotation and perspective-taking skills are also important (Lathan and Tracey 2002;

Menchaca-Brandan et al. 2007). Teleoperation is sufficiently difficult that several hundred hours of training are required to qualify, and all operations are monitored by a second qualified operator, backed up by a team of trainers and engineers on the ground. Recency is important, so ISS astronauts perform on-orbit refresher training.

Despite all the training and precautions, however, there were several significant ISS teleoperation incidents (e.g., collisions with a payload bay door, significant violations, or close calls) over the course of the first 16 ISS increments (Williamson 2007). Procedures are updated after each incident, but there are generic common factors relating to spatial visualization skills, misperception of camera views, timeline pressures, and fatigue.

g. Rover Performance

Driving a vehicle is one of the most complex sensorimotor/cognitive tasks attempted by most humans, and driving performance is known to be impaired in vestibular patients (Cohen et al. 2003). Page and Gresty (1985) reported that vestibular patients experience difficulty in driving cars, primarily on open, featureless roads or when cresting hills, and MacDougall and Moore (2005) reported that the vertical vestibulo-ocular reflex contributes significantly to maintaining dynamic visual acuity while driving. Adaptive changes in sensorimotor function during spaceflight can compromise a crewmember's ability to optimize multi-sensory integration, leading to perceptual illusions that further compromise the ability to drive under challenging conditions. During the Apollo Medical Operations Summit in Houston, TX (Scheuring et al. 2007), Apollo crewmembers reported that rover operations posed the greatest risk for injury among lunar surface EVA activities. During rover operations, crewmembers often misperceived the angles of sloped terrain, and the bouncing from craters at times caused a feeling of nearly overturning while traveling cross-slope, causing the crewmembers to reduce their rover speed as a result (Godwin 2002). While automatic control systems can compensate for some deficiencies in performance, lessons learned from the Apollo missions (Mindell 2008) suggest that manual takeover is required as a minimum safeguard, and therefore countermeasures must concentrate on mitigating risks associated with crewmembers in the control loop for rover operations.

h. Lunar surface operations

Prior to their missions the only 1/6 g vestibular stimulation crewmembers received was during limited parabolic flight training. After a 4.3 - 4.6 -day transit to the moon, lunar surface operations began between 4 and 15 hours after landing. Apollo EVAs were all in daylight, and on relatively flat terrain. There were no reports of significant disorientation or vestibular disturbances (Homick and Miller 1975). However, crews generally felt a little "wobbly" upon stepping on the moon. Coordination seemed to improve steadily during the first couple of hours on the surface. Falls were not uncommon and were attributed to rocks under the surface dust, equipment, terrain features, suit center of gravity (CG), and fatigue (Scheuring et al. 2007). Recovery from falls was met with varying degrees of difficulty, and repeated falls were fatiguing. Heart rate was often elevated during "rest periods." High suit CG, rigid torso, and lower ground reaction forces made walking on slopes more difficult (Goswami et al. 2021b). Surface topography and shadow contrast made it difficult to estimate slopes and judge distances (Oman 2007a).

During the 6 Apollo missions on the Moon, 12 crewmembers performed 14 EVAs that lasted a total of 78 hours. During these 14 EVAs, there were 23 falls and 11 saves. The causes and consequences of these falls obtained from video analysis and from crew reports are indicated in Table 1.

Apollo	Falls	Saves	First EVA	EVA Durations	Comments
11	0	0	6.4 h	EVA1= 2.5 h	- Tendency to tip over on high jumps, but no problems overall
12	2	0	4.6 h	EVA1= 3.9 h EVA2= 3.8 h	- Never fell down flat, able to roll over and push themselves up
14	0	1	5.4 h	EVA1= 3.9 h EVA2= 4.6 h	- Grabbed MESA before falling, no balance or stability problems overall - one-sixth g training helped them out
15	3	5	15.0 h	EVA1= 6.6 h EVA2= 7.2 h EVA3= 4.8 h	- Problems hopping down the ladder - Tripped on soft soil while taking pictures and on rocks - Concerned about getting dirty when pushing up - Lost balance while throwing a used pallet - Not worried about suit tears during falling, more concerned about rocks and unevenness - fell climbing steep soft rim of Station 6 crater - Potential for falling while down on one knee
16	10	4	14.4 h	EVA1=7.2 h EVA2=7.4 h EVA3= 5.7 h	- Loss of balance at Rover seat tugging of Velcro - Problems retrieving objects from lunar surface (rock, bag, dust, brush, penetrometer) - stumbled and ran forward to keep from falling - landed heavily on PLSS during jumping turn
17	8	1	4.0 h	EVA1=7.2 h EVA2=7.6 h EVA3= 7.3 h	- Problems retrieving objects from lunar surface (tool, rock) - Fall with discuss-like throw of bag - Problems removing deep core with jack - Fall getting on Rover and running across a slope

Table 1. Lunar EVA falls and close calls.

Timing of the first EVA based on mission report time of lunar touchdown contact to time of cabin depressurization (3 psia per telemetry data). The initial EVA on Apollo 15 was preceded by a “standup EVA” to take pictures and on Apollo 16 by a 8 hr rest period.

2. Evidence from Scientific Investigations During Human Spaceflight

This report was organized to present spaceflight evidence in three separate sections including space operations in Section V.A.1, inflight scientific investigations in Section V.A.2 and entry and post-flight investigations in Section V.A.3. Neurovestibular experiments have been conducted as early as the Vostok-3 mission in 1962 (Reschke et al. 2007b). The challenges of conducting investigations during the resource constrained missions have limited the evidence from these inflight studies. The most significant investments in terms of equipment and mission resources were conducted during the Skylab missions (M-131, Graybiel et al. 1977) and the Shuttle program, with studies on International Space Station (ISS) limited to simple laptop systems. As reviewed in this section, there were significant investments by NASA to examine inflight adaptation throughout the short-duration Shuttle program. The short-term adaptative changes are striking, although long-duration crewmembers readily acknowledge more subtle longer-term effects that either improve over the first several months, e.g., efficiency in movement control, while other effects can remain or reoccur throughout their mission. Examining longer term inflight adaptative changes remains a gap in our spaceflight evidence.

a. Space Motion Sickness

Space motion sickness (SMS) is the most clinically significant neurosensory phenomenon experienced by crewmembers during the first few days of spaceflight (Lackner and Dizio 2006). The neurosensory and motor systems and their relationship with the vestibular system were extensively studied during the early Shuttle missions. The major focus during that time was the prevention of SMS, which is characterized by a plethora of symptoms, such as somnolence, vomiting, stomach awareness, fatigue, and performance decrements.

Symptoms

On Earth, exposure to provocative motion, whether real or apparent, leads to the progressive cardinal symptoms of terrestrial motion sickness, which typically include the following: pallor, increased body warmth, cold sweating, dizziness, drowsiness, nausea, and vomiting. Although similar, the symptoms associated with SMS differ slightly from those of acute terrestrial motion sickness, probably because of differences in the physical environment, such as the lack of normal air-current vection and of gravitational force on the contents of the stomach. In particular, sweating, except for palmar sweating (Oman et al. 1990), is uncommon during spaceflight, and flushing is more common than pallor. SMS, as compared to acute terrestrial motion sickness, typically is more often associated with stomach awareness, vomiting, headache (due perhaps to headward fluid shifts), impaired concentration, lack of motivation, and drowsiness (Davis et al. 1988; Oman et al. 1990; Thornton et al. 1987b). Vomiting is usually sudden, infrequent, and is often not marked by prodromal nausea. Bowel sounds, obtained by auscultation, are decreased or absent in crewmembers experiencing SMS (Harris et al. 1997; Thornton et al. 1987a). Despite these differences, nearly universal symptoms are malaise, anorexia or loss of appetite, lack of initiative, and (for some) increased irritability.

Incidence

Historically, as the size of space vehicles has increased, so has the incidence of SMS. No SMS was reported in either Project Mercury or Project Gemini (Homick 1985), but 35% of the Apollo Program astronauts and 60% of the Skylab Program crewmembers developed symptoms of SMS (Davis et al. 1988). The incidence of SMS was 67% among first-time flyers on the first 24 Space Shuttle flights. Statistically, symptom occurrence was not different between career vs. non-career astronauts, commanders and pilots vs. mission specialists, different age groups, or first-time vs. repeat flyers. Also, an astronaut's susceptibility to SMS on his or her first flight correctly predicted susceptibility on the second flight in 77% of the cases (Davis et al. 1988). Later estimates indicated that 80% to 90% of all Shuttle crewmembers experienced some symptoms of motion sickness (Bacal et al. 2003).

Russian researchers report that 54% of cosmonauts have symptoms lasting 1 to 3 days, 25% have symptoms lasting 14 days or longer, and 8 of 46 cosmonauts on long-duration missions (85-365 days) periodically developed vertigo and queasiness, especially during the last 10 to 14 days of the mission, when their activity increased (Bryanov et al. 1986; Kornilova 1995). Symptoms of space motion sickness lasting the whole duration of the flight were observed during Shuttle missions (Reschke and Clément 2018).

Upon transition to microgravity on ISS missions, female astronauts have reported a slightly higher incidence of SMS (50%) compared with men (38%). However, these differences are not statistically significant, likely due to the small sample size of the female astronauts within this dataset (Mark et al. 2014; Reschke et al. 2014).

Provocative Stimuli

Microgravity by itself does not induce space sickness. The larger a volume of spacecraft and the mobility of their inhabitants, the higher chance of SMS. Specifically, factors that may initiate or worsen SMS include distasteful, unpleasant, or uncomfortable sights, noxious odors, certain foods, excessive warmth, loss of 1-g orientation, and head or whole-body movements (Jennings 1998). Similarly, post-flight symptoms may be induced and/or exacerbated by warmth and head movements during reentry and immediately after landing. Hypersensitivity to angular head motions is also common; crew members have reported that head movements in the pitch plane are initially more provocative than those made in other planes (Oman et al. 1990; Thornton et al. 1987b). In the only on-orbit systematic study of provocative stimuli (referred to as the M-131 study), crewmembers were immune to Coriolis cross-coupled stimuli on a rotating chair during the Skylab mission perform on or after flight day 8, i.e., after early inflight SMS had subsided (Graybiel et al. 1977).

Theories and Hypotheses

Many theories and hypotheses have been proposed to explain SMS (Lackner and Dizio 2006). The *fluid shift* theory (Barrett and Lokhandwala 1981; Parker et al. 1983) postulates that headward fluid shifts accompanying weightlessness produce changes that alter the response properties of vestibular receptors. However, this theory is not ideal in that it fails to adequately address the development of motion sickness during spaceflight.

The *sensory conflict* theory from Reason & Brand (Reason and Brand 1975) assumes that human orientation in three-dimensional space, under normal gravitational conditions, is based on at least four sensory inputs (otolith organs; semicircular canals; visual system; and touch, pressure, and somatosensory systems) to the CNS. Motion sickness may result when the environment is altered in such a way that information from sensory systems is not compatible and does not match previously stored neural patterns. It is important to note that it is the combination, rather than a single course, of these conflicts that somehow produces sickness, although the exact physiological mechanisms remain unknown.

In the *poison* theory, Treisman (Treisman 1977) suggested that the purpose of mechanisms underlying motion sickness, from an evolutionary perspective, was not to produce vomiting in response to motion, but to remove poisons from the stomach. Money et al. (Money 1996; Money 1970) concluded that the mechanism to facilitate vomiting in response to toxins is partly vestibular.

The *otolith mass asymmetry* hypothesis describes a mechanism complementary to the sensory conflict theory that explains adaptation to weightlessness, readaptation to 1 g, and individual differences in susceptibility to SMS (Kornilova 1983; Shelhamer et al. 2020; Von Baumgarten and Thumler 1979; von Baumgarten et al. 1982). According to this theory, some individuals possess slight functional imbalances between right and left otolith receptors that are compensated for by the CNS in 1 g. *Sensory compensation (Parker and Parker 1990)* occurs when the input from one sensory system is attenuated and signals from others are augmented.

The *Otolith Tilt-Translation Reinterpretation (OTTR)* hypothesis assumes that because of the fundamental equivalence between linear acceleration and gravity, graviceptors signal both the head orientation with respect to gravity (tilt) and a linear acceleration of the head that is perceived as translation. As a consequence of the absence of sensed gravity during orbital flight, graviceptors do not respond to static pitch or roll in weightlessness; however, they do respond to linear acceleration. Because stimulation from gravity is absent during spaceflight, interpretation of the graviceptor signals as tilt is meaningless. Therefore, during adaption to weightlessness, the brain reinterprets all graviceptor output to indicate translation (Parker et al. 1985; Young et al. 1984). The *sensory compensation* and *OTTR* hypotheses have both been further refined by Merfeld (2003) and Clément & Reschke (2008).

Recent studies have pointed out that individual susceptibility to motion sickness is related to the spatial-temporal properties of the vestibular system through the activation of the velocity storage mechanism (Lackner 2014). At lower rotation frequency, the velocity storage mechanism maintains spatial orientation by prolonging the nystagmus response beyond the end organ response. It is believed that this velocity storage mechanism increases the sensory conflict between actual and expected motion by increasing low frequency vestibular inputs and consequently triggers motion sickness (Clément and Reschke 2008).

Predicting Susceptibility

The prediction of susceptibility to motion sickness has long been of interest to spaceflight researchers. Since most motion sickness treatments are more effective when they are administered before symptoms develop, the identification of individuals susceptible to SMS would allow preventive measures to be taken only by those requiring them, and would free insusceptible persons from the undesirable side effects of anti-motion sickness medications and/or the scheduling requirements of pre-training (Diamond and Markham 1991).

A number of predictors for motion sickness have been investigated and can be grouped into the following categories: exposure history, physiological predisposition, psychological predisposition, plasticity, provocative tests, and operational measures (Clément and Reschke 2008). The real test of any predictive method relies on the use of data from crewmembers. Ground-based measures on normative subjects, while useful, are not true measures of the criterion of interest, SMS. Until enough flight data become available, along with ground-based tests for flight personnel, the relationships between various predictors and SMS susceptibility will remain unclear (Cassady et al. 2018).

Part of the difficulty in predicting motion sickness is the lack of a terrestrial vestibular analog (see section V.B). Another challenge is the operational nature of the environment wherein crewmembers actively using pharmaceutical countermeasures or alter activities (e.g., head movements) that would confound any systematic investigation. Nevertheless, some of the most promising terrestrial predictors include reversing prisms (Oman et al. 1986), torsional disconjugacy (Markham and Diamond 1993), and exposure to sustained centrifugation (Nooij et al. 2007). For now, the only reliable predictor of susceptibility is motion sickness experienced during a previous spaceflight.

b. Sensation

Visual Acuity

Testing of Mercury, Gemini, and Apollo astronauts revealed few significant changes in visual function with the exception of the following: constriction of the visual field, changes in intraocular tension, and changes in the caliber of retinal vasculature. Some constriction of the visual field was noted post-flight as well as a decrease in unaided seven-meter visual acuity, although the latter was not statistically significant. Post-flight decrease in intraocular pressure was significant and returned to preflight levels more slowly than expected. Retinal photography revealed no lesions but did show a decreased size of retinal vessels (Clément and Reschke 2008; Clément 2011).

Anecdotal reports from early Shuttle crewmembers describing decreases in visual performance, such as difficulty in reading checklists and unstable focus in the cabin, led to additional ophthalmologic testing (Task and Genco 1987). In 1989, NASA incorporated a questionnaire into the post-flight eye examination, regarding subjective reports of in-flight visual changes during short- and long-duration spaceflight. Astronauts were queried as to whether they perceived a subjective improvement or degradation in distant or near vision. This post-flight survey of approximately 450 astronauts (including several who had one or more previous flights) documented that visual changes were commonly experienced, particularly during long-duration spaceflight, with degradation in near vision being significantly more prevalent (Figure 2).

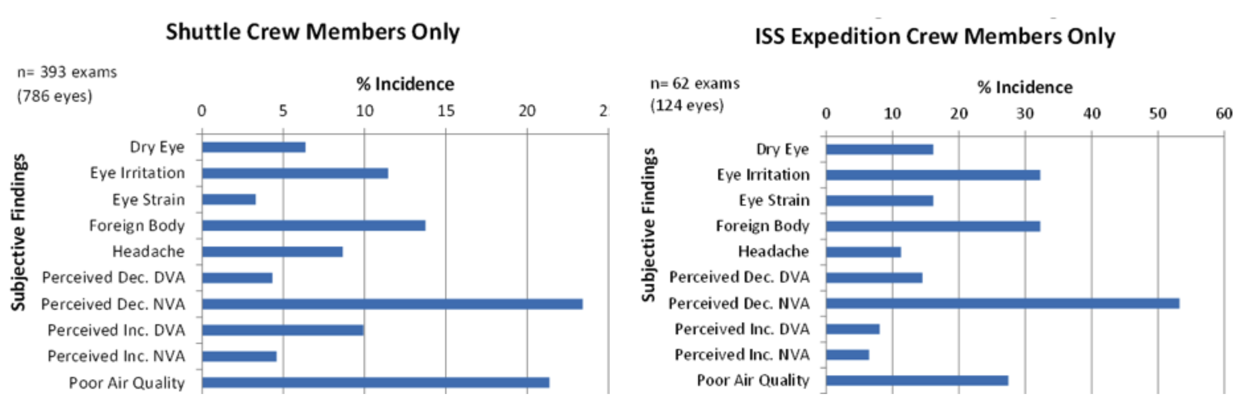


Figure 2. STS and ISS ocular findings

Anecdotal ocular findings among Shuttle (left) and ISS crewmembers (right) from post-flight questionnaire. (DVA=distance visual acuity; NVA=near visual acuity; Dec=decrease; Inc=increase)

These near vision changes were noted to be hyperopic (farsighted) in nature and more clinically apparent in older astronauts with decreased lens accommodation (Ginsberg and Vanderploeg 1987). In response to documented anecdotal reports of changes in near vision during spaceflight, astronauts over the age of 40 are prescribed “Space Anticipation Glasses” in the event that they experience a hyperopic shift during the mission. This visual shift appears to occur gradually, is variable in magnitude, and may persist for years following return to Earth. The origin of the visual changes during spaceflight is thought to be posterior globe flattening and choroidal engorgement brought about by cephalad fluid shifts leading to a forward displacement of the retina. This shortening of the distance between the retina and the lens may account for the hyperopic shift in microgravity (Mader et al. 2011; Mader et al. 2013).

Proprioception

Microgravity modifies the stimuli associated with proprioception and thus affects the astronauts’ knowledge of the position of their limbs (Kornilova 1997; Reschke et al. 1986; Schmitt 1985). Altered proprioception has been observed to cause erroneous discrimination of mass while accelerating a ball up and down using whole-arm movements (Ross et al. 1984). Mass discrimination improves, however, with arm movements of higher acceleration, an indication that the in-flight impairment is partly due to a reduction in the z-axis pressure stimulation that provides information about weight on Earth (Ross et al. 1986a; Ross et al. 1986b).

Two theories exist to explain the observed decrements in proprioceptive function: (a) a physical degradation in the proprioceptive sensory system either via neural fiber degeneration, muscle atrophy, fluid shift, or the sudden and prolonged release of a constant muscle tone; (b) a disturbance of an external or internal-based spatial map. The results of pointing experiments suggest that gravity is important for the maintenance of a stable external spatial map (Berger et al. 1997; Watt 1997; Young et al. 1993). An egocentric reference system may also be used to assess limb position and maintain a sense of verticality (Kurtzer et al. 2005; Lackner and DiZio 2005b). This was observed aboard Mir when cosmonauts were able to draw ellipses in the air, either parallel or perpendicular to the longitudinal axis of the body, without visual aid. However, conflicting results have suggested there is a body scheme disturbance in the absence of gravity (Berger et al. 1992).

Proprioceptive illusions generated by vibrating leg muscles are different in-orbit compared to preflight. The perceptual effect of vibrating leg muscles was investigated in two subjects restrained on a back support. Before flight, leg vibration induced either a backward or forward tilt sensation depending on which muscle was vibrated. After 20 to 21 days in orbit, the same vibrations caused a different whole-body sensation. When the back support was used to replicate the axial force of normal gravity, the preflight illusions of forward and backward tilt returned (Roll et al. 1993). The results from a similar setup in parabolic flight demonstrated that illusory movements were diminished in weightlessness but increased in hypergravity relative to 1 g. The authors concluded that the receptor output per unit stretch of a muscle spindle is influenced by variations in gravitational strength suggesting that unloading the otoliths in freefall decreases their descending modulation of alpha and beta motor neurons. This results in decreased tonic vibration reflexes (Lackner and DiZio 1992).

Proprioceptive illusions that involve self- or surround-motion have been observed for several muscle groups. The type and magnitude of illusion is influenced by the duration of spaceflight, the use of tactile cues, and whether the subject is restrained or free-floating (Lackner 2021). When crewmembers, each wearing a special harness, were dropped from a quick-release hook, the sensation was one of the floor coming up rather than the subject falling. Most subjects reported that the floor suddenly slapped them on the feet (Reschke et al. 1984). The stretch reflex resulting from this landing propelled the subjects higher in the air than the height from which they were originally dropped.

However, there was a large variability in individual perception styles. Some subjects felt anchored by tactile cues from bungee cord-induced foot pressure, while others felt a tendency toward self-rotation under the same circumstances (Watt et al. 1992; Young et al. 1993). The CNS system that compares motor commands with sensory inputs may not be able to correctly distinguish between self-motion and movement of the environment because of sensory reinterpretation that occurs in spaceflight (Jones 1974; Lackner 2021; Parker et al. 1985; Reschke et al. 1986; Reschke and Parker 1987; Young et al. 1984).

Motion Perception

Some cosmonauts have reported sensations of linear acceleration to occur after engine cut-off (Bryanov et al. 1986; Kornilova 1983; Kornilova 1995). The change in threshold for detecting linear acceleration during flight, during passive body motion using a sled or another crewmember, has been hard to determine (Arrott and Young 1986; Arrott et al. 1990; Benson and Vieville 1986; Young et al. 1993). Considerable variability was seen across crewmembers between the in-flight and pre-flight responses. Threshold sensitivity does seem to be axis- and gravity- dependent, but the difference in unloading the saccular and utricular otolithic membranes has yet to be fully addressed (Clément and Reschke 1996).

During passive angular acceleration in orbit, perception of the angle of rotation was overestimated during both roll and pitch movements (Clément et al. 1987). Yaw was not affected because, much like on Earth, the otoliths do not play a large role in yaw stimulation (Armstrong et al. 2015). Using a multi-axis rotating chair to assess subjective response to passive angular motion in orbit, results showed that pitch motion resulted in a perceived tumbling sensation. One subject reported that roll rotation felt like yaw motion (Benson et al. 1986). Without a constant gravitational vector or visual cues, the subject's reference to the environment is established using intrinsic coordinates. If no sensory map is available to establish intrinsic coordinates, then the axis of rotation or orientation relative to extrinsic coordinates cannot be determined (Harm et al. 2015; Wright et al. 2006).

Rotating-dome experiments conducted during Spacelab missions showed that most subjects experienced increased intensity in their visually induced sensation of motion (called vection) in microgravity, with some reporting complete rotatory (saturated) vection during flight (Young et al. 1986; Young and Shelhamer 1990). The onset of linear vertical vection in free-floating cosmonauts was earlier than in ground-based tests. Subjects also reported the illusion of bending forward and pitch, rather than linear vection (Mueller et al. 1994). Visual-induced illusions become stronger in space, perhaps because the otolith organs neither confirm nor deny body tilt in microgravity.

c. Gaze Control

Eye-head coordination is critical to performing piloting tasks, and it is very important to controlling other vehicles (e.g., rovers and automobiles) and complex systems (e.g., robotic arms and other remote manipulators). Rapidly locating and reading instrument displays, identifying suitable landing locations, free of craters, rocks, etc., and tracking the motion of targets and/or objects being manipulated are among the tasks requiring good vision enabled by optimized eye movement control (Harm et al. 2007). A large body of evidence demonstrates that the G-transitions associated with spaceflight disrupt oculomotor performance. Highlights are summarized in the following subsections.

Smooth Pursuit Eye Movements

Smooth pursuit eye movements are produced during voluntary visual tracking of moving targets without head movements. Evidence suggests that the basic mechanisms underlying smooth pursuit tracking are modified by exposure to spaceflight. When crewmembers were asked to visually track a simple point stimulus at 0.33 Hz in either horizontal or vertical planes, the amplitude of eye movement was reduced, and the number of corrective saccades was increased (Kornilova et al. 1991a; Kornilova et al. 1991b; Reschke et al. 1996; Reschke et al. 1999). They crewmembers clearly undershot the target. The performance deterioration was the most pronounced for a point stimulus moving vertically or diagonally, early in-flight (flight day 3), late in flight (flight days 50, 116, and 164), and early after flight. Thus, it appears that the saccadic system must be utilized extensively to maintain accurate target tracking, and vision is degraded by an inability to maintain the target focused on the fovea (Hopp and Fuchs 2006).

Vestibulo-Ocular Reflex

During head and/or body movements, the gaze stabilization system maintains high visual acuity by coordinating movement of the eyes and head to stabilize the image of interest on the fovea. The vestibulo-ocular reflex (VOR), a servo system that uses head motion signals sensed by the semicircular canals and otolith organs to generate vision-stabilizing compensatory eye movements, is critical to this function. Blurred vision, oscillopsia (illusory movement of the visual world), and/or reduced dynamic visual acuity occur when this gaze compensation mechanism is disrupted. VOR function is plastic, meaning it can adapt to different environmental stimuli (Berthoz and Melvill Jones 1985). For example, the VOR gain (amount of eye rotation caused by a unit of head rotation) adapts when individuals begin wearing new prescription eyeglasses. A number of relevant flight experiments have demonstrated that various VOR response properties are modified during and after spaceflight and that the degree of adaptation varies among subjects and experimental conditions (Reschke et al. 1996).

No significant changes in yaw VOR gain were observed in response to voluntary (active) head oscillations at frequencies ranging from 0.25 to 1 Hz (Benson and Vieville 1986; Thornton et al. 1985; Thornton et al. 1988; Thornton et al. 1989; Vieville et al. 1986; Watt et al. 1985). Unlike yaw plane head movements, pitch and roll plane head movements in normal gravity change the orientation of the head relative to the gravity vector, thereby modulating gravitational stimulation of the otolith organs (Wood et al. 2009). One might expect, therefore, that the pitch and roll plane VOR would be more affected by spaceflight than the yaw plane

VOR. The pitch VOR response to voluntary head oscillations has been measured during and after spaceflight at frequencies comparable to those described above for yaw, and the results are inconclusive. Some studies have reported no changes inflight (Watt et al. 1985), while others found an increase VOR gain and in the phase lag (delay between head motion and elicited eye motion) (Berthoz et al. 1986), yet others reported a decrease in vertical VOR gain (Clarke et al. 1993; Vieville et al. 1986). Clarke et al. (Clarke et al. 2000) also reported changes in torsional VOR during voluntary head movements in the roll plane during and after spaceflight.

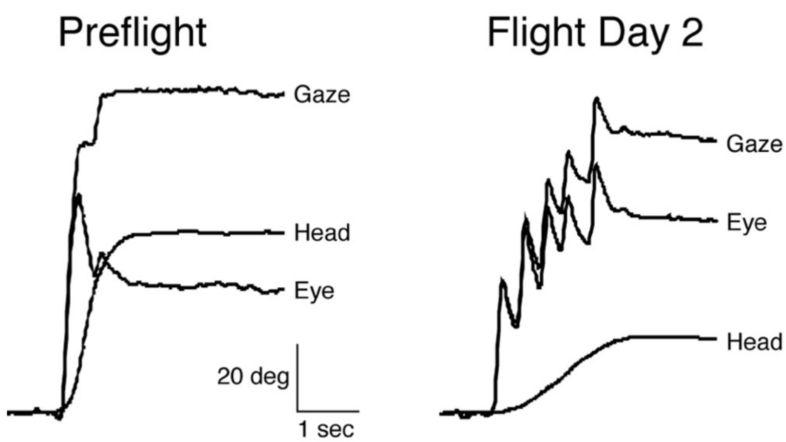
These findings suggest that VOR is presumably disrupted early after insertion into orbit. Fortunately, central adaptive processes re-establish VOR response properties over time in the new environment, resulting in recovery of accurate stabilization of vision during head and/or body movements in said environment. However, critical mission activities requiring accurate gaze stabilization during head movements (e.g., piloting/landing a spacecraft) will likely be performed less skillfully during or soon after G-transitions. During one case study involving the longest Spaceflight mission on record (438 days on Mir EO-15), the torsional VOR gain in dark was initially enhanced early inflight and gradually decreased throughout the mission (Clarke and Kornilova 2007). More recent eye movements recorded on ISS have been limited to visual-vestibulo-ocular reflexes since recordings were performed in the light. During one study, gradual changes in Listing's plane (defined by the three-dimensional orientation of the eye and its axes of rotation) over a period of 6 months were inferred to represent a reduction of the torsional VOR component (Clarke et al. 2013).

Eye-Head Coordination and Target Acquisition

Gaze is the direction of the visual axis in three-dimensional space. It is defined as the sum of eye position with respect to the head and head position with respect to space. Acquisition of new visual targets of interest is generally accomplished using coordinated eye-head movements consisting of a saccadic eye movement that shifts gaze onto the target combined with a VOR response that maintains the target on the fovea as the head moves to its final position. Spaceflight modifies eye-head coordination during target acquisition (Kozlovskaya et al. 1985; Thornton et al. 1988; Tomilovskaya et al. 2011) and ocular saccadic performance (Andre-Deshays et al. 1993; Reschke et al. 1996; Reschke et al. 1999; Uri et al. 1989).

Different strategies for gaze and target acquisition have been observed during and post-flight. Head movement towards a target near or beyond (≥ ±50°) the effective oculomotor (EOM) range is delayed, resulting in a VOR that tends to pull gaze off target (Reschke et al. 2017b; Reschke et al. 1999). Reduced angular positioning of the head forces larger compensatory eye saccades to direct the eye back to the target (Gresty and Leech 1977; Zangemeister et al. 1991; Zangemeister et al. 1988; Zangemeister and Stark 1981; Zangemeister and Stark 1982) (Figure 3). The slower head movement contributes to a near doubling of the latency required to fixate peripheral targets. Sirota et al. (1987) showed that during adaptation to space, non-human primates trained to perform a visual target acquisition task requiring accurate perception of peripheral targets showed delays in the onset of the gaze response and made significantly more errors in identifying the visual characteristics of the peripheral targets.

Between 1989 and 1995, NASA evaluated how increases in flight duration of up to 17 days affected the health and performance of Space Shuttle astronauts. Thirty-one Space Shuttle pilots participating in 17 space missions were tested at 3 different times before flight and 3 different times after flight, starting within a few hours of return to Earth. The astronauts moved their head and eyes as quickly as possible from the central fixation point to a specified target located 20°, 30°, or 60° off center. The mean time to visually acquire the targets immediately after landing was 7–10% (30–34 ms) slower than mean preflight values, but results returned to baseline after 48 hours. This increase in gaze latency was due to a decrease in velocity and amplitude of both the eye saccade and head movement toward the target. Results were similar after all space missions, regardless of length (Reschke et al. 2017b).



Eye, head, and gaze (sum of eye and head) position during target acquisition 50° in the horizontal plane. Note that on the second flight day the head rotation is delayed, the head moves at a much lower velocity than preflight, and the VOR is infused with several saccades to bring the eye on target.

Figure 3. Sample of early inflight target acquisition

Optokinetic Nystagmus

Optokinetic eye movements that are produced in response to scene motion, whether it is induced by self-motion or surround-motion, offer a unique way to investigate the effects of spaceflight on the vestibular system, as the vestibular cells in the brainstem integrate visual scene movement and head movement relative to the environment. The asymmetry in optokinetic nystagmus (OKN) gain normally observed on Earth was reversed during the first 3 days of spaceflight and a downward drift was still evident on the fifth day, despite the gain and the eye movement field being nearly normal. A decrease in vertical OKN gain was also noted during flight, which increased shortly after flight, along with a restoration of asymmetry (Clément and Berthoz 1988; Clément and Berthoz 1990). An experiment using short-radius centrifugation to elicit linear acceleration in orbit also indicated that the eye rotation axis during OKN tended to align with this linear acceleration (Moore et al. 2005a; Moore et al. 2005b). The reduced vertical asymmetry might reflect adaptation from a gravitational to an idiotropic reference frame in situations where vertical asymmetries have no functional use (Dai et al. 1994).

d. Eye-Hand Coordination Performance

Eye-hand coordination skills are also critically important to performing piloting tasks and controlling other vehicles and complex systems. Reaching to switches on instrument panels, smoothly guiding the trajectory of a flight- or ground-based vehicle, and carefully positioning the end-effector of a robotic arm are some of the tasks requiring high levels of eye-hand coordination (Bortolami et al. 2008). While not studied as intensively as oculomotor performance, a number of studies of eye-hand coordination have been performed during spaceflight missions.

Control of Aimed Arm Movements

When astronauts first encounter an altered gravity environment, arm movements are often inappropriate and inaccurate (Gazenko et al. 1981; Johnson et al. 1975; Nicogossian et al. 1989). During the Neurolab Space Shuttle mission (STS-90), Bock et al. (Bock et al. 2003) performed an experiment in which subjects pointed, without seeing their hands, to targets located at fixed distances but varying directions from a common starting point. Using a video-based technique to measure finger position they found that the mean response amplitude was not significantly changed during flight, but that movement variability, reaction time, and duration were all significantly increased. After landing, they found a significant increase in mean response amplitude during the first post-flight session, but no change in variability or timing compared with preflight values. In separate experiments, Watt et al. (Watt et al. 1985; Watt 1997) reported reduced accuracy during spaceflight when subjects pointed to memorized targets. This effect was much greater when the hand could not be seen before each pointing trial. When subjects pointed at memorized locations with eyes closed, the variability of their responses was substantially higher during spaceflight than during control sessions on Earth. In other studies (Berger et al. 1997; Papaxanthis et al. 1998), the investigators found that when crewmembers on the Mir station pointed to targets with eyes open, variability and mean response amplitude remained normal, but the movement duration increased by 10 to 20% over the course of the mission (flight day 2-162).

Reaching and Grasping

Thornton and Rummel (1977) showed that basic tasks such as reaching and grasping were significantly impaired during the Skylab missions. Later, Bock and colleagues (Bock 1996; Bock et al. 1996a; Bock et al. 1996b; Bock and Cheung 1998; Bock et al. 1992; Hudson et al. 2005) investigated pointing, grasping, and isometric responses during brief episodes of changed gravity, produced by parabolic flights or centrifugation. These experiments provided converging evidence suggesting that during either reduced or increased gravity, the mean amplitude of responses is larger than in normal gravity, while response variability and duration remains unchanged. During the Neurolab Space Shuttle mission, Bock et al. (2003) found that the accuracy during flight of grasping luminous discs between their thumb and index fingers was unchanged from preflight values, but task performance was slower. During the same mission, astronauts initiated ball catching movements earlier in 0 g than in 1 g, suggesting that in some contexts the brain uses an internal model of gravity to supplement sensory information when estimating time-to-contact (McIntyre et al. 2001). Further experiments on ISS have shown that crewmembers appropriately adjusted throwing speed and the catching time when imagining object motion in 0g or 1 g, suggesting that mental imagery of these types of tasks may be useful for inflight training (Gravano et al. 2021). Recent studies by McIntyre, Thonnard, and colleagues have demonstrated distinct adaptation patterns between grip dynamics and arm kinematics in different gravity environments and are currently conducting similar studies on the ISS (Opsomer et al. 2021; White et al. 2018).

Manual Tracking

Changes in the ability of crewmembers to move their arms along prescribed trajectories have also been studied in space. For example, Gurfinkel *et al.* (1993) found no differences in orientation or overall shape when crewmembers with eyes closed drew imagined ellipses oriented parallel or perpendicular to their long body axes. In another study, Lipshits *et al.* (1993) examined the ability of crewmembers to maintain a cursor in a stationary position in the presence of external disturbances. They found no performance decrements when the disturbances were easily predictable. However, in follow-on experiment using more complex disturbances, Manzey and colleagues (Manzey et al. 1998; Manzey et al. 1995) found that tracking errors were increased early in flight but gradually normalized within 2-3 weeks of exposure to the space environment. Step-tracking performance accuracy was also affected only marginally during flight in another experiment (Sangals et al. 1999). However, kinematic analyses revealed a considerable change in the underlying movement dynamics: too-small force and, thus, too-low velocity in the first part of the movement was mainly compensated by lengthening the deceleration phase of the primary movement, so accuracy was regained at its end.

In another experiment wherein subjects tracked with their unseen finger a target moving along a circle at 0.5, 0.75, or 1.25 Hz, subjects' response paths were found to be elliptical rather than circular (Bock et al. 2003). The variability of finger positions about the best-fitting ellipse was significantly higher than preflight during the first in-flight session, and responses lagged significantly behind the target during the highest target speed condition. Performance normalized later during flight, but deficits, albeit less pronounced, reappeared during the first two post-flight test sessions. It should be noted that response slowing and increased variability were limited to the first in-flight session for the tracking paradigm but were most pronounced during later in-flight sessions for the pointing paradigm. The investigators interpreted these observations as indicating an underestimation of mass during flight (Bock et al. 2003).

Force Discrimination and Control

During a Mir station mission, the ability of a cosmonaut to reproduce several positions of a handle from memory was tested. The accuracy with which the handle was set to a given position was reduced. However, the temporal parameters of the movement and the number of discernable handle positions did not change (Lipshits et al. 1993; Reschke et al. 1996).

Fine Motor Control

During the one-year ISS mission (Charles and Pietrzyk 2019), Holden and colleagues observed small but reliable decrements in fine motor control early inflight during pointing tasks, dragging tasks, and shape tracing tasks on a tablet (Holden et al. 2020). Campbell *et al.* (2005) evaluated the feasibility of survival surgery performed on rats during the Neurolab Shuttle mission. Craniotomy, leg dissection, thoracotomy, laminectomy, and laparotomy were performed as a part of physiological investigations. Surgical techniques successfully demonstrated in rats during spaceflight include general anesthesia, wound closure and healing, hemostasis, control of surgical fluids, operator restraint, and control of surgical instruments. Although the crew noted no decrement in manual dexterity, the operative time was longer compared with the ground experience due to the need to maintain restraint of surgical supplies and instruments. In another study, Rafiq et al. (2006) measured the effect of microgravity on fine motor skills by investigating basic surgical task performance during parabolic flight. They found that forces applied to the laparoscopic tool handles during knot tying were increased while knot quality was decreased during flight compared with ground control sessions. Also, Panait *et al.* (2006) studied the performance of basic laparoscopic skills (clip application, grasping, cutting, and suturing) during parabolic microgravity flights. When compared with one gravity performance, they found that there was a significant increase in tissue injury and task erosion with a decreased trend in the number of tasks successfully completed.

Dual-Tasking and Manual Performance

Dual-tasking may be more impaired during or immediately following periods of G-transitions since vestibular alterations can impact attention and cognitive processing ability (Bigelow and Agrawal 2015), especially related to spatial memory (Smith 2021). While experimental evidence for cognitive deficits during spaceflight is somewhat equivocal (Manzey 2017), dual-task/divided-attention paradigms have been more sensitive to change (Strangman et al. 2014). There are a number of stressors during spaceflight that impact cognitive processing (Stahn and Kuhn 2021); however, cognitive overload may be higher when complex motor skills are required around periods of greater adaptative change (Bock et al. 2010). Studies have demonstrated the effects of dual tasking (a cognitive and motor task) on manual control during spaceflight. Manzey et al. (1998) found impairments in tracking performance and time-sharing efficiency during the first month in space. These impairments included larger single- versus dual-task differences of both memory search speed and tracking error in orbit compared to preflight. Bock et al. (2010) also found more tracking error for dual-task conditions inflight compared to preflight. Importantly, the increase in tracking error persisted for the duration of the mission and did not recover until four days after the return to Earth. Manzey et al. (1995) examined dual task performance for a crewmember throughout an 8-day space mission. Specifically, unstable tracking with concurrent memory search was tested 13 times during the course of the mission. The results indicated impairments in the single task memory and dual task performance. Based on the results from these studies, psychomotor processes and higher attentional functions are impaired when in the space environment.

Laboratory tasks might underestimate the actual deficits since they differ from a real-life scenario in a number of ways. For example, the slowing of aimed arm movements was 10-30% in experimental tasks but was up to 67% during routine activities on Skylab as analyzed using time and motion studies (Kubis et al. 1977). Degradation of performance may be exacerbated in part due to postural instability, which may not play a role when a pilot controls a landing while strapped into a seat but may have a greater impact if landing is performed while standing like during the Apollo lunar landings.

e. Spatial Disorientation

Spatial disorientation has been one of the most frequently studied aspects of sensorimotor adaptation during spaceflight (Parmet et al. 2021). Astronauts report that the most overt physiological phenomena associated with spaceflight are inversion illusions at main engine cut off, occasional in-flight disorientation, early-mission motion sickness, and head-movement-contingent disorientation during entry and landing. These neuro-vestibular phenomena occur during and after G-level transitions, which, unfortunately, also correspond to mission phases where physical and cognitive performance are particularly critical for crew safety and mission success. Accurate perception of self-in-space motion and self-motion relative to other objects are critical to piloting, driving, and remote manipulator operations.

The literature on spatial disorientation (SD) events during spaceflight has been well reviewed (Oman 2003; Oman 2007b). Numerous detailed firsthand accounts by astronauts and cosmonauts have also appeared (Burrough 1988; Cooper 1976; Hadfield 2013; Jones 2006; Linenger 2000; Lu 2003). Almost all crewmembers describe a transient somatogravic tumbling illusion or momentary inversion illusion upon reaching orbit when main engine cutoff causes a rapid deceleration to constant orbital velocity. About 10% subsequently experience a sense of gravitational inversion (what they call “the downs”) that persists for 2 to 3 days after launch regardless of relative body orientation in the cabin, even with eyes closed. Persistent inversion illusions are thought to result from the combined somatosensory effects of headward fluid shift and saccular otolith unweighting (Graybiel and Kellogg 1967; Mittelstaedt 1986a; Mittelstaedt 1986b; Mittelstaedt 1987; Oman et al. 1986).

On Earth, the ability to perceive verticality is quite good. This ability is dependent on input from visual, vestibular and somatosensory systems, and on a functioning CNS (Bortolami et al. 2006a; Bortolami et al. 2006b; Bryan et al. 2007; Ozdemir et al. 2018). Many reports also exist of astronauts’ perceptions of pitch-forward, pitch-up, or pitch-down attitudes once they enter weightlessness (Harm and Parker 1994), giving rise to an altered subjective vertical. The perception of subjective visual vertical was investigated in cosmonauts on short- and long-duration flights, either seated upright or rolled laterally (Bokhov et al. 1969; Bokhov et al. 1973; Kornilova and Kaspransky 1994). Absolute errors in estimates of orientation in the roll plane were significantly improved during one ISS pilot study using vibrotactile feedback (van Erp and van Veen 2006).

Clément et al. (1987) examined in-flight adaptive changes in perception of subjective body orientation. They observed that when subjects' feet were held in Shuttle foot restraints, perception of subjective body orientation depended greatly on visual cues. Rotation around the ankle joint had little or no effect on correcting tilt angle in the absence of vision, which may be related to the lack of proprioceptive input during static limb positioning. The flexor tone produced in the dorsiflexor muscles has been proposed to help maintain a virtual vertical projection of the body’s center of mass (Massion et al. 1997). In other words, the CNS tries to recreate a condition in weightlessness that is like that on Earth. This interpretation agrees with an internal representation of gravity (Clément et al. 2001b; Mittelstaedt and Glasauer 1993), which allows a coherent mental representation of the body in alignment with the longitudinal axis. This internal model of gravity would also serve as a reference frame for movement.

Visual Reorientation Illusions

The Visual Reorientation Illusion (VRI) has been first described by astronauts on the Skylab and Spacelab-1 missions. When crew float about in the cabin, they experience a spontaneous change in the subjective identity of surrounding surfaces, such that the "surface beneath my feet seems somehow like a floor." Oman (Oman 2003; Oman 2007b) noted that astronauts must orient with respect to a vehicle frame of reference defined by local visual vertical cues. However, architectural symmetries of the cabin interior typically define multiple "visual vertical" directions, usually separated by 90˚. The Earth can provide yet another visual reference frame when viewed through cockpit windows or while spacewalking. There is a natural tendency to perceive the subjective vertical as being aligned with the head-foot axis, generally referred to as the "idiotropic" effect (Mittelstaedt and Mittelstaedt 1996). Which visual reference frame the observer adopts thus depends strongly on relative body orientation and visual attention. VRI occur when the perceived visual vertical reference frame is not aligned with the actual, so that, for example, the overhead surface is perceived as a deck.

The type and magnitude of perceptual illusions may depend on whether a crewmember uses an idiotropic or visual reference frame. Individuals who are visually oriented with respect to external references perceive themselves to be inverted or sideways during flight. They report difficulty in switching rest frames and performing coordinate transformations, in addition to experiencing loss of orientation in the absence of visual cues. When an idiotropic reference frame is used, the alignment of a vertical along the longitudinal body axis allows little disorientation and an easy switch between rest frames. Forty-six percent of astronauts and 58% of cosmonauts were classified as using an idiotropic reference frame, 46% of astronauts and 34% of cosmonauts as using predominantly visual reference, and 8% of both crews were classified as using a mix of both (Friederici and Levelt 1990; Harm and Parker 1993; Young et al. 1986). Individual experiences with self- or surround-motion may vary, but commonly reported illusions include (a) exaggerated rate, amplitude, and positioning of body movement; (b) temporal disturbance to perception of motion; and (c) altered path perception (Harm et al. 1999).

Data from animal experiments in parabolic and orbital flight (Oman 2007b; Taube et al. 2004) suggest that the VRI surface identity illusion physiologically corresponds to a realignment of the two-dimensional plane that limbic neurons use to code direction and location. When VRI occur, crews lose their sense of direction with respect to the entire vehicle and reach or look in the wrong direction for remembered objects. Susceptibility to VRI continues through the first weeks in space, and occasional illusions have been reported after many months on orbit. Strong sensations of height vertigo have been described during spacewalks. These might reflect sudden changes in the limbic horizontal frame of reference from the spacecraft to the surface of the Earth.

VRI can also occur on Earth, but reorientations usually occur only in yaw perception about the gravitational axis, e.g., when we emerge from a subway and discover we are facing in an unexpected direction. VRI about Earth-horizontal axes have been created using tumbling rooms and virtual reality techniques (Harm et al. 2008). For example, investigators have shown that the direction and strength of visual vertical cues depend on field of view, the relative orientation of familiar gravitationally "polarized" objects, and the orientation and symmetry of surfaces in the visual background (Howard and Hu 2001; Hu et al. 1999; Jenkin et al. 2007). Single planar surfaces or the longer surface in a rectangular room interior were most frequently identified as “down” (Oman 2007b). Prior visual experience and knowledge of the specific environment are also important factors. Even when VRI do not occur, the visual verticals of adjacent or docked spacecraft modules are often incongruently aligned. Astronauts typically orient to the reference frame of the local module, and significant cognitive effort is required to sort out these multiple vehicle frames of reference. Using virtual reality simulations, Oman and Aoki (Aoki et al. 2007; Aoki et al. 2006; Oman 2007b) have shown that subjects remember the interiors of each module in a canonical, visually upright orientation. When performing tasks that require subjects to interrelate different reference frames, additional time is required, and workload imposed. The fastest responses occur when module verticals are congruently aligned. Significantly greater time is required to perform simulated emergency egress navigation tasks when module visual vertical reference frames are incongruently aligned (Oman et al. 2006).

Tilt-Translation and Tilt-Gain Illusions

Arguably the greatest spaceflight-related challenge to the human internal navigation system results from the ambiguities between tilt and translation stimuli. Einstein (Einstein 1908)Einstein (Einstein 1908) was the first to postulate “the complete physical equivalence of a gravitational field and a corresponding acceleration of the reference system.” According to his equivalence principle, linear accelerations resulting from translational motions are physically indistinguishable from linear accelerations resulting from tilts with respect to gravity because the forces are identical in nature. The ability of the central nervous system to resolve tilt-translation ambiguities is critical to providing the spatial orientation awareness essential for controlling activities in everyday life.

Two hypothetical mechanisms that have been proposed for resolving tilt-translation ambiguities are frequency segregation and multi-sensory integration. The “frequency segregation hypothesis” suggests that low frequency linear accelerations are interpreted as tilt and high frequency accelerations as translation (Mayne 1974; Merfeld et al. 2005). This hypothesis appears consistent in principal with the response dynamics of the different primary otolith afferents (Fernandez and Goldberg 1976; Fernandez et al. 1972; Peterson and Chen-Huang 2002), secondary processing of otolith input in the vestibular nuclei (King et al. 1999; Xerri et al. 1987), and also with natural behavior (Pozzo et al. 1990). The “multi-sensory integration hypothesis”, on the other hand, suggests that the brain must rely on information from other sensors, such as canals and vision, to correctly discriminate between tilt and translation (Angelaki et al. 1999; Guedry 1974). More specifically, it suggests that the brain learns to anticipate a sequence of sensory feedback patterns for any given movement. This hypothesis generally involves the use of internal models, or neural representations of physical parameters, and combines efferent and afferent information to resolve sensory ambiguity (Droulez and Darlot 1990; Green and Angelaki 2004; Oman 1982; Poon and Merfeld 2005; Young 1974; Zupan and Merfeld 2005; Zupan et al. 2000).

Although multi-sensory integration and frequency segregation are typically posed as competing hypotheses, they are not mutually exclusive. The segregation of otolith-ocular responses as a function of frequency has been clearly demonstrated (Paige et al. 1996). Yet one implication of frequency segregation is that there must be a mid-frequency crossover region where it is difficult to distinguish tilt from translation. Paige and Seidman (Paige and Seidman 1999) reported that the crossover frequency is approximately 0.5 Hz in primates, and Wood (Wood 2002) suggested that it occurs at about 0.3 Hz in humans. Multi-sensory integration may play a critical role near the crossover frequency.

Among the factors that facilitate sensorimotor adaptation, active voluntary motion may be one of the most important (Welch 1986). Performing visual tasks with the intent to override vestibular input may also catalyze adaptation (Guedry 1964; Shelhamer and Beaton 2010; Shelhamer and Beaton 2012). Most sensory conflict theories related to sensorimotor adaptation have been derived from the concept of "efference copy", which states that there are predicted sensory feedbacks for any given motor action (Reason 1978; von Holst and Mittelstaedt 1973). Head movement kinematics on Earth yield invariant unique patterns of canal and otolith signals irrespective of other sensors (Guedry et al. 1998). During adaptation to altered gravito-inertial environments, though, new patterns of sensory feedback must become associated with head movements to reduce sensory conflict. The observation that some astronauts tend to restrict head-on-trunk movements on orbit, preferring to rotate more from the waist than the neck, reflects an adaptive change in motor strategy that might further contribute to motion sickness (Watt 1997) and post-flight postural and dysfunction (Bloomberg et al. 1997).

Two separate human experiments conducted on orbit by Reschke et al. (Reschke et al. 1988) and Clément et al. (Clément et al. 2001b) investigated the effects of sustained linear accelerations during eccentric rotation created by short-radius centrifuges. Interestingly, subjects reported no sense of translation in either experiment during the constant velocity centrifugation. In orbit exposure to 0.2 Gz at the head during 60 s of constant velocity was insufficient to provide a vertical reference (Benson et al. 1997), possibly because of the opposing G-gradient along the trunk and legs and/or the relatively small resultant force level (Mittelstaedt 1999). When subjects were exposed to greater force levels (0.5 Gy and 1.0 Gz) for up to 5 min, these forces did provide a vertical reference on orbit. The subjects perceived roll-tilt when the resultant force was directed along the interaural axis and inversion when the resultant force was directed towards the head (Clément et al. 2001b). Ocular counter-rolling was also unchanged during this experiment (Moore et al. 2001).

f. Decrements in Cognitive Function

Controlling vehicles and other complex systems can place high demands on cognitive and psychomotor functions. Spaceflight might affect these functions through direct microgravity effects (such as those described in the preceding sections) or through stress effects associated with sleep loss, workload, or the physical and emotional burdens of adapting to the novel, hostile environment. Kanas & Manzey (2003) provide a thorough overview of the relevant evidence. As should be clear from that which is presented here, spaceflight induces many of the hallmarks of compensation from vestibular disorder (Lacour et al. 2016). Cognitive deficits, such as poor concentration, short-term memory loss, and inability to multi-task occur frequently in patients with vestibular abnormalities (Jacob and Furman 2001; Jacob et al. 1996; Lawson et al. 2016). Reviews of the literature suggest (Hanes and McCollum 2006; Smith 2021) broader interactions between vestibular and cognitive function (including oculomotor, motor coordination, and spatial perception/memory effects like those described above) and demonstrating a physiological basis through observations of neuronal projections from the vestibular nuclei to the cerebral cortex and hippocampus. These results suggest that cognitive abilities may be most compromised shortly following G-transitions, particularly if an off-nominal event occurred that had not been recently well-rehearsed. In the following sections the results of spaceflight investigations on the mental representation of space (mental rotation, three-dimensional visual perception, distance perception) are reviewed.

Mental Rotation

The face of a well-known person is not as easily recognized when presented upside down. This phenomenon suggests that people have difficulty recognizing familiar shapes when they are in an unfamiliar orientation (Cohen 2000; Finke and Shepard 1986; Howard 1982; Howard and Templeton 1966). In such circumstances, mental rotation is necessary for shape and facial recognition. Until crewmembers become adept at mentally rotating themselves and/or their environment, and/or develop new spatial maps, they can easily become disoriented. Poor ability to mentally rotate the visual environment could be an important factor in determining susceptibility to space motion sickness (Parker and Harm 1992).

Mental image rotation and reconstruction experiments were performed on orbit. During STS-51G, mental reconstruction after body tilt demonstrated that the critical angle was 65°, which is comparable to values attained on Earth (Corballis et al. 1978). After 3 days of microgravity, the subjects could mentally rotate the environment even while they were in an inverted position (Clément et al. 1987). The investigators proposed that mental rotation could be a gravity-dependent process and that weightlessness, by releasing this constraint, facilitates processing of visual images in any orientation. In contrast, Léone et al. (Leone et al. 1995) suggested that mental rotation depends on symmetry detection and an internal vertical reference. In the absence of gravity, detection of symmetry was less accurate and required more time. The discrepancies between findings may be attributed to procedural differences, use of subject restraint, and difficulty of mentally manipulating test objects.

Experiments using mental rotation of three-dimensional objects (Shepard and Metzler 1971) in the yaw and roll axes, while subjects were restrained, showed that response times and error rates were similar before and during flight. Similarly, cube rotation response time improved from pre- to post-flight, likely attributable to practice effects from performing the task multiple times onboard the ISS (Tays et al. 2021). These results were consistent with those of Friederici & Levelt (Friederici and Levelt 1987; Friederici and Levelt 1990) and Léone et al. (Leone et al. 1995) and support the conclusion that mental rotation of visually presented 3-D objects is independent of gravity.

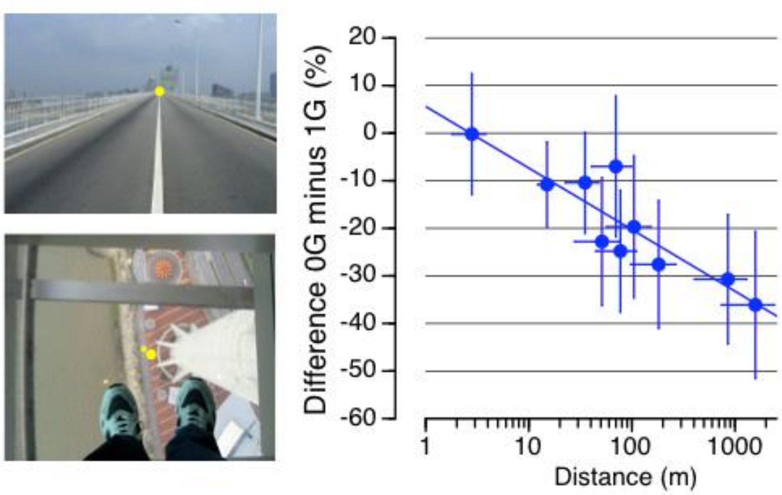
Distance and Size Perception

Further spaceflight-related changes occur in cognitive visual-spatial processing, which helps in perception of distance and size of objects. Distance and size perception are skills learned through repetitive practice. Normally sighted, binocular and even totally monocular people develop and use effective distance and size perception skills (Beaton et al. 2015). Monocular depth cues include angular variations—or parallax—when moving the head; texture, luminosity, color, and shading variations of the visual scene; and perspective.

In microgravity, the environment is not structured with a gravitational reference and a visual horizon, so perspective is less relevant. Astronauts perceive heights and depths of objects as taller and shallower on orbit, respectively (Clément et al. 2013; Lathan et al. 2000). In microgravity, the astronauts perceived apertures to be wider or themselves to be smaller compared to normal gravity (Bourrelly et al. 2016). There are also changes in the perception of geometric illusions and perspective-reversible figures after 3 months in space (Clément et al. 2015a; Clément et al. 2012). These changes may occur because the perspective cues for depth are less salient in microgravity (Clément et al. 2015a).

Ground-based studies also showed that the occurrence of geometric illusions based on perspective is reduced when subjects are tilted relative to the gravitational normal (Clément and Eckardt 2005) and in patients with vestibular deficits (Clément et al. 2009). Consequently, the changes in 3D visual perception in orbit reduction are presumably due to the altered peripheral otolith input or to a central adaptation in the processing of visuo-spatial cognitive function (Clément and Reschke 2008).

On Earth, horizontal distances relative to the observer are accurately estimated up to 4 m and underestimated by approximately 10% as distance increases (Daum and Hecht 2009). By contrast, vertical distances are overestimated by about 30%, especially when looking down (Stefanucci and Proffitt 2009). During a recent study, 6 astronauts were presented with stereoscopic (anaglyphs) photographs of natural scenes. Small yellow targets were superimposed on easily recognizable landmarks within each scene, e.g., a remarkable building, the end of a bridge, the top of a mountain, or the bottom of a tower. The subjects were asked to estimate the absolute distance between themselves and the target (egocentric distance) using a conventional metric of their choice (e.g., feet, yards, or meters). On average, the astronauts reported distances above 50 m to be about 20%-25% smaller in-flight than pre-flight (Figure 4). One interpretation for this underestimation of distance in flight is that the distance between the eyes and the floor varies when astronauts are free floating; therefore they cannot use the eye height scaling to estimate distance as on Earth (Clément et al. 2013).



Differences in egocentric distance estimations using natural scenes between inflight and preflight conditions (Clément et al. 2013).

Figure 4. Differences in size perception during ISS

Because size perception is related to distance perception, a follow-up study compared the astronauts' abilities to evaluate the size of objects on Earth and in orbit. This experiment was performed with the astronauts free-floating and in darkness, which eliminated somatosensory and visual orientation cues. When astronauts adjusted the size of a cube so that it looked normal in orbit, they made its height shorter and its depth longer than on Earth, which means that a perfect cube was perceived as taller and shallower (Clément et al. 2013).

There are two possible interpretations for these results: (a) it is the impairment in the processing of gravitational input that is responsible for the observed alteration in the mental representation of space in the astronauts in microgravity or (b) the confinement inside the ISS is responsible for the changes in size and distance estimates, especially for distances that are larger than the internal dimensions of the ISS modules.

It is interesting to note that no changes in distance perceptions were observed with the Mars500 crewmembers who spent 520 days in a confined mock-up of a space station in Moscow (Šikl and Šimeček 2014). These crewmembers had no difficulties in perceiving depth in geometric illusions. Also, their estimation of object's size appropriately reflected the scale of a visual scene displayed on a computer display. Information that was contained in the far distance remained as salient as information in the near distance. Only their visual space seemed to be compressed in the in-depth dimension relative to the frontal dimension, but this effect could have been due to the visual stimuli that were not displayed in stereoscopic vision.

Distortions of the visual space during space missions may influence astronauts' ability to accurately perform cognitive and sensorimotor tasks, such as those involved in robotic operations. Additionally, this misperception will alter how astronauts view their habitat and workspace volume. These are important considerations for future human planetary exploration missions and warrant further investigation and consideration for countermeasure development (Clément et al. 2013).

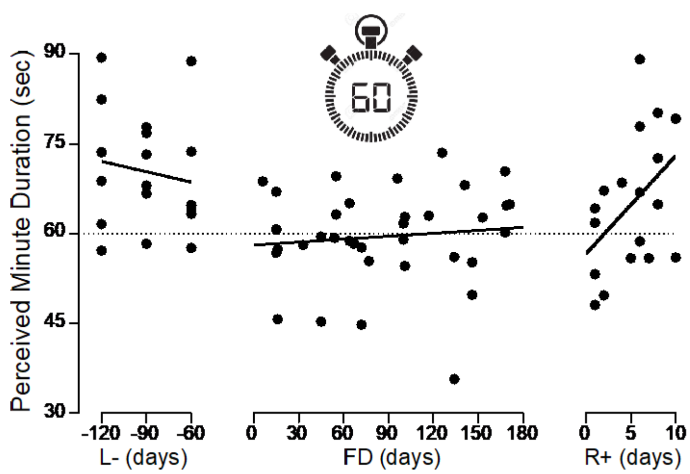
Time Perception

The conditions of spaceflight, including weightlessness, prolonged isolation in confined areas, limited mobility, significant overloads, etc., are known to affect human physiological and psychological responses. These conditions may alter temporal relationships as well. Some astronauts and cosmonauts have reported a "time compression syndrome" in orbit, whereby time is subjectively sensed as compressed relative to the perceptions gained during training and simulation (Albery and Repperger 1992; Schmitt 1985). Another perception experienced by the astronauts is that longer time than normal is required to execute standard mental activity (Manzey et al. 1998). Yet another reported syndrome is "space fog", which affects cognitive performance during the first weeks of a mission (Welch et al. 2009).

Following the historical one-orbit flight of Yuri Gagarin, Gherman Titov flew on board Vostok-2 for a full day (17 Earth orbits) and performed the first cognitive neuroscience experiments in orbit. The objective of one experiment was to assess his ability to evaluate time intervals. After starting a stopwatch, he began to count 20 s in his mind; when he estimated subjectively that 20 s had passed, he stopped the stopwatch and looked at the actual elapsed time. The average time estimates during the 4 in-flight sessions were not significantly different from those measured during training, but they were biased by the fact that he had continuous feedbacks on his performance (Leonov 1969).

Another experiment on time perception in microgravity was performed on four astronauts during a 4-day Space Shuttle mission. Subjects viewed a visual target traversing a display and, while it was obscured, estimated the time of its arrival at a predetermined point by any means other than counting. The time perception for short duration tasks (2 s) were consistently overestimated in 0 g. As the time duration of the task increased, the subjects tended to underestimate. These errors in duration estimates increased each day as the flight progressed. Three hours after landing the duration estimates were also significantly larger than on flight day 4 (Ratino et al. 1988). These results suggest that the ability to estimate brief intervals of time deteriorate during a short space mission and after landing.

Another study of time perception is currently being performed on ISS astronauts (protocol as in Clément 2018). The preliminary results indicate that the perceived duration of one minute was clearly underestimated in orbit compared to preflight (Figure 5). Also, astronauts underestimated time intervals of 2-5 hours and 1 month during spaceflight. However, they quite accurately estimated the number of days since vehicle dockings and spacewalks. Prolonged isolation in confined areas, stress related to workload, and high-performance expectations are potential factors contributing to altered time perception of daily events.



Perceived duration of one minute before (L-), during (flight days, FD) and after (R+) spaceflight in six astronauts.

Figure 5. Difference in time perception on ISS

Similar alterations of time perception were also observed in subjects exposed to hypergravity in a centrifuge (Albery and Repperger 1992). The authors point out that one potential consequence of these effects is that crewmembers who need to make quick decisions and perform critical tasks in-flight and re-entry may exhibit some delays in their responses, which would compromise safety.

Cognition Test Batteries

A cognitive test battery has been used by the medical operations to monitor for untoward events, medical conditions, or the cumulative effects of spaceflight that negatively affect an astronaut's neurocognitive status (WinSCAT, Kane et al. 2005). A newer computerized cognitive test battery (*Cognition*) based on tests known to engage specifically these brain regions is currently being used on the ISS as part of Spaceflight Standard Measures. *Cognition* consists of 10 simple neuropsychological tests that cover a range of cognitive domains, including emotion processing, spatial orientation, and risk decision-making (Basner et al. 2015). In addition to providing neuroimaging-based novel information on the effects of spaceflight on a range of cognitive functions, *Cognition* will facilitate comparing the effects of ground-based analogues to spaceflight, increase consistency across projects, and thus enable meta-analyses. Ground-based tests suggest that performance in some domains such as processing speed may explain some of the variance in performance on complex sensorimotor tasks like docking performance (Basner et al. 2020).

g. Neural Changes Associated with Spaceflight

Section V.C. reviews evidence of neural changes with spaceflight from animal studies. Human neuroimaging investigations have been limited to pre- and postflight testing (Section V.A.3 below). In-orbit electroencephalography (EEG) studies have suggested that the brain uses dynamic sensory reweighting based on incoming sensory information during spaceflight. Cheron et al. (Chéron et al. 2006) used EEG to examine alpha and mu brain oscillations in cosmonauts while in eyes-opened and eyes-closed states before, during, and after spaceflight. During in-flight EEG recording sessions, Cheron et al. (Chéron et al. 2006) found increases in alpha and mu power during trials in which cosmonauts rested in an eyes-closed state. This finding suggests an increase in sensory gain for inputs from other modalities (e.g., vestibular or somatosensory) in the absence of visual input.

Cheron *et al.* (Cheron et al. 2014) have also demonstrated that spaceflight affects early visual processing. EEG data were acquired in-flight while astronauts viewed a two-dimensional checkerboard pattern and a three-dimensional tunnel. During spaceflight, visual evoked potentials triggered by the three- dimensional stimulus were suppressed, and occipital brain areas exhibited reduced alpha band activity. The authors suggested that interactions with brain areas involved in multisensory integration modulate early visual processing, reweighting sensory inputs in the absence of gravitational cues (Cheron et al. 2014).

3. Evidence from Scientific Investigations during Reentry and after Landing

Physiological changes that optimize function in microgravity are typically maladaptive for return to earth's gravity. Since brief exposures to accelerations during G-profile training or aborted launches do not elicit the same constellation of re-entry signs and symptoms (McGregor et al. 2021a), sensorimotor decrements upon returning to Earth's gravity largely reflect the adaptation to novel patterns of sensory cues experienced during motion on orbit (Wood et al. 2011). Results from re-entry and post-flight scientific studies presented in this section represent a major source of the sensorimotor evidence. As with inflight changes, the data demonstrates broad intersubject variability in terms of both severity and time course of recovery. Flight duration isis a major factor. Other factors include type of landing (Shuttle versus capsule, land versus water), activity required during the landing and egress, and the procedural resources available to stabilize the crew. Heat stress, dehydration, orthostasis (fainting upon standing), sleep deprivation and exhaustion are commonly observed and may increase post-flight susceptibility (Ortega et al. 2019).

a. Re-entry motion sickness and perceptual changes

No reports of post-flight motion sickness (PFMS) were noted in the Space Shuttle program through the mid-1980s (Thornton et al. 1987b). However, it now appears that this syndrome affects a similar percentage of both U.S. and Russian crews. The Russian reports indicate that PFMS symptoms generally occur in cosmonauts who have SMS in-flight. However, 11% of those who experience little or no SMS on orbit do experience mal de débarquement (Bryanov et al. 1986). Postflight medical debriefs were examined for Shuttle missions from the beginning of the program, in April 1981, through January 1999, which involved 241 crewmembers having flown between one and six missions. Postflight, 32% of crewmembers reported vertigo, 14.7% reported nausea, and 8% vomiting (Bacal et al. 2003). The incidence was greater for longer Shuttle flights (Jennings 1998) and for long duration crewmembers returning from the International Space Station (ISS) as confirmed by recent Field Testing (Reschke et al. 2017a; Reschke et al. 2020b). Long duration Field Test participants reported motion sickness ratings during testing (using the scale described above) with a median score of 14 (range 3-20) in the medical tent. During this initial medical tent testing, 15% of these participants did not attempt any tests and 32% stopped testing before completing. Post-flight symptoms are alleviated by medications (e.g., meclizine), restriction of early activities, and intravenous fluid therapy. While none of the 12 Apollo astronauts reported motion sickness during lunar descent and EVAs, as stated above their incidence of in-flight motion sickness appears lower than average. Several Apollo crewmembers pre-medicated prior to Earth re-entry, and the majority experienced motion sickness following the water landings (Scheuring et al. 2007). One Apollo crewmember noted dizziness or light-headedness that persisted for 7 days following recovery (Homick and Miller 1975).

PFMS onset occurs in a time pattern similar to that of SMS. Within minutes of g-force onset during re-entry, symptoms may already be developing. Crewmembers who have no symptoms during re-entry and landing may develop symptoms as soon as they stand up to exit the vehicle. The severity of the symptoms and the functional recovery seem to be directly proportional to the time on orbit. There have been reports of a “relapse” phenomenon in the post-landing recovery course. Astronauts who are exposed to certain types of inertial environments, like turning a corner in a car or lying in bed in the dark, can bring on a sudden return to an early postflight state of maladaptation, which may elicit ‘mild’ to ‘severe’ PFMS symptoms several days up to a week after return to Earth. Recovery from this “relapse” generally occurs more rapidly than the recovery immediately after returning from orbit (Ortega and Harm 2008).

Neurovestibular symptoms after Shuttle missions were captured using a standardized questionnaire (Bacal et al. 2003). It is important to keep in mind the subjective nature of these reports as well as the possibility that some crewmembers might not have reported truthfully for personal reasons. These symptoms include:

Clumsiness in movements (69%; n=410)
Difficulty walking straight line (66%; n=403)
Persisting sensation aftereffects (60%, n=324)
Vertigo while walking (32%; n=393)
Vertigo while standing (29%; n=397)

Nausea (14.7%; n=346); vomiting (8%; n=347)
Difficulty concentrating (10%; n=284)

Crewmembers also report a number of perceptual changes after spaceflight that may hinder their work performance: (a) *modified sensations of movement*, i.e., a feeling that they or the visual surroundings are moving following a simple head movement in any plane; (b) *sensations of excessive body weight* up to 2 to 2.5 times normal weight or that *objects, when handled, are heavier than normal*; (c) *sensations of greater bodily tilt* when the body is tilted from the vertical axis; and (d) *sensations of forced movement* of the body when turning corners.

Most perceptual disturbances and other symptoms resolve rather quickly, within 48 hours. Others, such as postural ataxia, may last with varying degrees of effect for months. During this prolonged recovery phase, tasks that require integration of multiple sensory inputs, e.g., head tilts while on unstable support surfaces, often reveal an underlying deficit that may not be revealed with more restricted movements. Interaction with the environment can shorten recovery times. Like SMS, PFMS does not appear to correlate with age, crew position, or number of previous flights (Reschke et al. 2014). Past experience with postflight re-adaptation does not seem to affect incidence (Bacal et al. 2003). PFMS is likely complicated by the relative dehydration upon return and orthostatic intolerance following flight.

Sensitivity to provocative testing

As part of the Human Vestibular Function (M-131) study during the three Skylab manned missions, eight crewmembers performed head and body movements during yaw rotation ranging from 12.5-30 rpm (Graybiel et al. 1977). This stimulus generated Coriolis, cross-coupled accelerations, which were at the origin of motion sickness preflight. All crewmembers could perform more head body movements and had reduced motion sickness from flight day 6 and beyond. In addition, 7 out of the 8 crewmembers had reduced motion sickness postflight from the day after landing (R+1) through R+17. The remaining crewmember had mild and severe MS for two of the 3 days at sea following splashdown. The other crewmembers had taken anti-motion sickness medication taken during recovery and reported no motion sickness.

Other experiments demonstrated that most subjects perceive passive vestibular stimulation to be less provocative on landing day than preflight. For example, 9 of 10 crewmembers tested had no symptoms of motion sickness when exposed to passive yaw rotation or Coriolis acceleration on R+0 (Clément et al. 1999; Oman et al. 1996; Thornton et al. 1987b). In those experiments using passive rotation on R+1 and later, 26 out of 29 crewmembers showed a decreased of susceptibility to MS postflight relative to preflight (Graybiel and Knepton 1977; Harm et al. 1994; Moore et al. 2001; Wetzig et al. 1993). One crewmember was tested using Coriolis and off vertical axis rotation (OVAR) following the 10-day Apollo-9 mission. Reports indicated that the single subject tested had an average susceptibility to motion sickness preflight and that there was an increase tolerance with repeated exposures postflight (Homick and Miller 1975). In another study, 58 crewmembers participating in 16 flights of the Space Shuttle (duration < 11 days) were also tested during Coriolis (12.5-30 rpm) and during OVAR (20 rpm up to 30° tilt) before (L-3 to L-6 months) and after (R+0 to R+3 months) their spaceflight. This experiment focused on predictive values of ground tests (Homick et al. 1987). Two crewmembers tested immediately postflight showed reduced motion sickness to Coriolis (up to several weeks), although one subject was found to be hypersensitive on landing day (Thornton et al. 1987b). Past experiments indicate that velocity storage (Cohen et al. 1977), the central integration of semicircular canal signals, is attenuated during exposure to nonterrestrial gravitoinertial force backgrounds and that this effect carries over to the postflight period (DiZio and Lackner 1988; Oman and Balkwill 1993; Oman et al. 1996). Converging evidence from ground-based and spaceflight experiment also points to a relation between motion sickness and the properties of the velocity storage (Dai et al. 1996; Dai et al. 2010; DiZio and Lackner 1991; Oman 1998). Perception of the vertical and of body angular movements indicate that spatial integration of canal afferent signals is disturbed after adaptation to microgravity (Clément et al. 2007; Clément et al. 2001b), suggesting that velocity storage is reduced.

Perceived Tilt and Translation

Crews typically report that when they tilt their heads, they feel that the “gain” of their head tilt sensation is increased, as if their head had rotated farther than expected. A typical pilot comment is, *“That really tumbled my gyros”.* The sensation is thus reminiscent of the conventional hypergravic G-excess illusion. Other returning astronauts describe a transient sensation of horizontal or slightly upwards linear translation as a result of head tilt (Harm et al. 1999; Parker et al. 1985; Reschke 1994). One of the most common post-flight illusions is of perceived translation, either of self or surround, during a tilting motion (Harm and Parker 1993). In one of the first post-flight experiments to investigate this phenomenon, a parallel swing was used to provide horizontal (interaural axis) translation and/or roll rotation about the head naso-occipital axis. All six astronauts participating in this study reported an increase in perceived lateral translation during passive roll rotation after flight (Reschke and Parker 1987).

On the basis of these observations, and similar ones reported by Young et al. (Young et al. 1984), the otolith Tilt-Translation Reinterpretation Hypothesis (OTTR) was proposed. The OTTR hypothesis is based on the premise that interpreting otolith signals as indicating tilt is inappropriate during spaceflight. Therefore, during adaptation to weightlessness, the brain reinterprets otolith signals as indicating translation only. Relevant to driving tasks on sloped terrains, it is interesting to note that performance during roll-tilt closed-loop nulling tasks is decreased for several days post-flight (Merfeld 1996), while performance during translation closed-loop nulling experiments appears to be improved (Arrott et al. 1990).

An alternative hypothesis proposed by Guedry et al. (Guedry et al. 1998) suggests that rather than a reinterpretation of otolith signals, adaptation to spaceflight might involve ‘shutting down’ the search for position (tilt) signals from the otolith system in order to avoid vestibular conflict. This is based on the observation that on Earth the initial head position relative to gravity before a head turn foretells the unique combination of canal and otolith signals that will occur during the turn. The absence of a meaningful initial position signal from the otoliths on orbit may therefore be functionally disruptive and eventually neglected. Guedry’s hypothesis also explains the post-flight tilt-translation disruptions described above, as well as the increased immunity to Coriolis stimuli observed following the Skylab missions (Graybiel and Knepton 1977).

Differences between active and passive motions may help explain some of the apparently contradictory observations regarding post-flight tilt-translation disturbances. For example, Golding et al. (Golding et al. 2003) observed striking differences in motion sickness sensitivity between active and passive tilts. It is likely that the new 'expected' patterns of sensory cues adopted during head tilts on orbit will differentially influence responses during reentry depending on whether the motion is self-generated.

Merfeld (Merfeld 2003) noted that the OTTR hypothesis assumes that the utricular otolith mediates all tilt sensation and that, if otolith cues were simply reinterpreted as linear acceleration, a sustained head tilt should produce a sustained acceleration sensation–not what is usually observed. He hypothesized that both types of illusions could result from a change in the effect of semicircular canal cues on estimating transient rotations of the direction of "down" relative to the head. Unless the CNS estimate of angular velocity is aligned with the estimated direction of gravity, a conflict occurs. His hypothesis, known as the Rotation Otolith Tilt-Translation Reinterpretation (ROTTR) hypothesis, suggests that the CNS resolves this conflict by rotating the direction of its internal estimate of gravity at a rate proportional to the vector cross product of the estimated angular velocity and gravity vectors. These rate constants determined the dynamics of the resulting illusion (Merfeld et al. 1993).

Tilt-translation illusions can occur during spacecraft pitching or rolling maneuvers, even if the pilot's head remains stationary relative to the cockpit, potentially leading to incorrect manual control responses. For example, a Tilt Gain illusion might result in an under-response to a Shuttle wing drop, a sensation that a wind gust was pushing the nose up unexpectedly, resulting in under-rotation during the critical landing flare maneuver. An OTTR illusion might produce an over-response to a wing-drop and perhaps the sensation that a gust had suddenly pushed the Shuttle off runway centerline. One implication of ROTTR theory is that the tendency toward Tilt Gain or OTTR illusions may be a personal characteristic. If so, this could account for the diversity in the anecdotal descriptions by astronauts.

Some evidence exists that provides insight into the physiological basis of these illusions. For example, in a series of rodent experiments, Ross (Ross 1993; Ross 1994; Ross 2000; Ross and Varelas 2003) showed increased numbers of synapses in type II hair cells of the utricular maculae during and just after spaceflight. The findings of increased synaptic plasticity are consistent with the human behavioral studies suggesting an increased gain of the otolith organs. These findings were also supported by an experiment performed by Boyle et al. (Boyle et al. 2001) aboard the Neurolab mission, in which the primary utricular afferent information was shown to be highly potentiated (up-regulated) during the first few hours after spaceflight in oyster toadfish (Opsanus tau) subjected to linear translations in various planes. These data were similar to those reported by Reschke et al. (Reschke et al. 1986), who found an enormous potentiation of the monosynaptic Hoffman reflex response early after flight in human subjects from the Spacelab-1 mission subjected to linear translational acceleration stimuli. This Hoffman reflex response, which is modulated by descending signals from the vestibular otolith organs and normally aids in preparing the anti-gravity muscles for stable landing following a jump (or fall), had completely disappeared in these same subjects by the sixth flight day of the mission.

Further evidence was obtained by Holstein & Martinelli (Holstein and Martinelli 2003), who found in rodents flown aboard the Neurolab mission ultrastructural signs of plasticity in the otolith recipient zone of cerebellar cortex (nodulus), an area thought to be critical for motor control, coordination, timing of movements, and motor learning. Rats flown for 5-18 days in the Russian Cosmos Biosatellite Program also showed morphological changes in neural structure, including decreased lengths in dendrites directed from cells in the reticular formation toward structures in the vestibular nuclei and morphological changes in cerebellar structures including mossy fiber terminals in the granular layer of the nodular cortex (Krasnov 1994). Pompeiano (Pompeiano 2003) also studied rodents flown aboard the Neurolab mission. He found biochemical evidence of plasticity (expression of the immediate early gene c-fos and presence of fos-related antigens) in multiple regions of the brain, including the vestibular nuclei, which play a role in controlling posture and eye movements, the nucleus of the tractus solitarius (NTS), which is involved in regulation of cardiovascular and respiratory function, the area postrema, which plays a role in motion sickness, the amygdala, cortical and subcortical areas involved in body orientation and perception, and the locus coeruleus, which is involved in regulation of the sleep-wake cycle.

Otolith Asymmetry

Another underlying mechanism that may contribute to inflight and postflight disturbances in perception and spatial orientation is natural asymmetry in otoconial mass between the right and left saccule and utricle. These asymmetries would lead to different output signals from the left and right otoliths. On Earth the CNS is thought to compensate for this inherent imbalance between otoliths. However, exposure to a weightless environment may lead to decompensation of this process, leading to asymmetrical output from the right and left otolith organs and subsequent disturbances in perception of motion and spatial orientation (Clarke et al. 2013). A study was conducted using Shuttle crewmembers that examined otolith asymmetries as a potential underlying factor contributing to inflight and postflight perceptual and motor control disturbances (Clarke et al. 2010). The study utilized both cervical vestibular evoked myogenic potentials (cVEMP) as an indicator of otolith saccular function through measurement of a vestibulo-collic reflex and unilateral centrifugation as a test of utricular function. Results showed a general increase in asymmetry of otolith responses on landing day relative to the preflight baseline data. There was a subsequent reversal in asymmetry within 2-3 days. Recovery back to preflight levels occurred within the first week following the return to Earth but appeared to return slower for the utricular responses (Clarke and Schonfeld 2015). These findings indicate that spaceflight results in adaptive changes in neural integration of otolith inputs contributing to perceptual illusions during gravitational transitions.

Proprioceptive Changes

Overall, the post-flight reports of increased heaviness of static objects suggest that some central rescaling of static pressure systems occurs. A Spacelab D-1 mission required subjects to use higher accelerative shaking forces, which improved their ability to discriminate mass but not weight. Additionally, video recordings of astronauts showed that shaking was faster in-flight compared to preflight and slowed after landing, returning to baseline after three days (Ross et al. 1986a). Error in weight or mass perception may be due to a basic failure of reafference or to inadequate monitoring of command signals and inappropriate scaling of afferent signals.

Evidence for proprioceptive adaptation with spaceflight includes post-flight changes in tactile sensitivity of the feet. Post-flight, there is a general reduction in the sensitivity of slow adapting skin receptors (3 and 25 Hz), which contribute to postural control on Earth by detecting load changes between the foot and ground (Lowrey et al. 2014; Strzalkowski et al. 2015). It is hypothesized that body unloading (i.e., that one's muscles are not needed to support their body weight) during flight makes this signaling less vital, and it is thus down-weighted by the central nervous system. Approximately half of the astronauts presented with increased sensitivity of fast acting skin receptors (250 Hz) post-flight. This hypersensitivity has been associated with poorer vestibularly mediated balance on the first day post-flight. It is hypothesized that this increase in post-flight tactile sensitivity represents adaptive targeted sensory reweighting, in which the altered gravitational environment during flight causes down weighting of vestibular inputs and up-weighting of signals from fast-acting tactile receptors for balance control (Ozdemir et al. 2018). That is, while in microgravity, these tactile receptors may play a larger role in orientation control as compensation for unreliable vestibular inputs.

b. Gaze Changes

Vestibulo-Ocular Reflex (VOR)

Evidence exists that the VOR could be severely compromised during the transition between low Earth orbit and the return to Earth's gravity. Using a gaze stabilization protocol, eye and head movements were recorded from crewmembers inside of the Landing and Entry Helmet during descent (Reschke et al. 1999). This protocol required the subject to view a target presented at a distance of approximately 0.5 m from the eyes. Immediately upon target presentation, vision was occluded, and the subject acquired the remembered target. One second later the target was exposed, and the subject made any correction to the target with only the eyes. This protocol permitted the determination of the VOR gain. Interestingly, the data showed that the VOR is not functional immediately after landing.

A system for rapid vestibulo-ocular assessment without measuring eye movements per se has been recently proposed. VON (vestibulo-ocular nulling) uses a head-mounted motion sensor, laptop computer with user input control, and a laser target. As the head moves, the target is made to move in the same manner with a gain set by the subject. When the subject sets the gain so the target appears stationary in space, it is stationary on the retinas. As a functional perceptual measure, VON accounts for gaze-stabilizing contributions that are not apparent in the standard VOR, such as pursuit and perceptual tolerance (Beaton et al. 2017).

Experiments during the D-1, SLS-1, and SLS-2 Spacelab missions utilized passive body movements provided by step changes in the angular velocity of rotating chairs to stimulate the VOR. During parabolic flight, the persistence of the yaw VOR response after the chair motion stopped was decreased in eight astronauts tested just before spaceflight (Oman and Balkwill 1993; Oman et al. 1996) and in normal subjects (DiZio and Lackner 1988). However, after 4-10 days in orbital flight, the yaw VOR persistence was no different from preflight values in five of the eight astronauts tested, although active head pitch movements ("dumping") did not interfere with the VOR persistence, as it consistently did on Earth. Early after flight (1-2 days), the persistence was decreased relative to preflight in nine of 12 astronauts tested, but it eventually returned to preflight values in all (Oman and Kulbaski 1988).

Another study indicated that subjects fixed their gaze on a visual target, or imagined this target when vision was occluded, during the gain and phase of the VOR when they voluntarily oscillated their heads around the yaw axis at 0.33 Hz or 1Hz in darkness. The VOR gain during fixation at both oscillation frequencies remained near unity for all trials. However, early inflight and immediately after the flight, VOR gain in darkness was lower than before the flight. The phase between head and eye position was not altered by spaceflight (Clément et al. 2019b).

The VOR gain was also examined during eccentric roll rotation before, during, and after an 8-day orbital mission. On orbit this vector is aligned with the head z-axis. On Earth, the stimulation primarily generated torsional VOR. During spaceflight, torsional VOR became horizontal VOR, and then decayed very slowly. The shift from torsional to horizontal VOR on orbit is attributed to a spatial orientation of velocity storage toward alignment with the gravito-inertial acceleration vector, and the inter-individual difference to cognitive factors related to the subjective straight-ahead (Reschke et al. 2017b).

These findings suggest that transitions to and from weightlessness temporarily reduce the contribution of brainstem mechanisms that normally extend the low frequency bandwidth of the human angular VOR response.

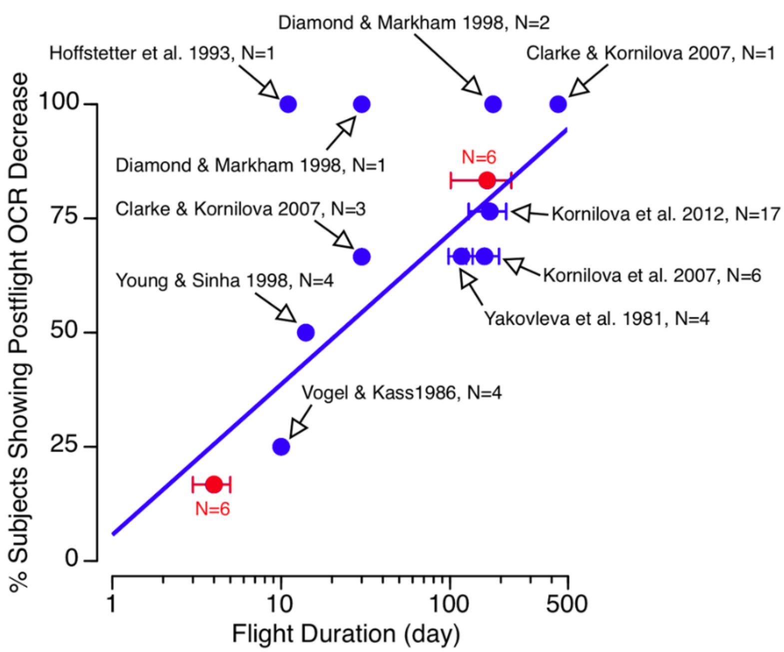
Ocular Counter Rolling

The otoliths, detectors of linear acceleration, contribute to eye stabilization and spatial orientation during spaceflight. In the absence of gravity, head tilt has insignificant meaning, and therefore torsional eye movements should be minimal or absent. However, statolith input may be reinterpreted. As a result, ocular counter-rolling (OCR) induced by tilt has been investigated before and after spaceflight as an indicator of otolith adaptation. Head tilt after Gemini missions induced no changes in OCR (Graybiel et al. 1967).

Clément et al. (Clément et al. 2007) have reviewed the evidence of changes in OCR during static whole body tilt in post-flight studies following Space Shuttle missions, and they noted that the findings are inconsistent. Some studies report decreases in astronauts' OCR after the flight relative to preflight, while others have shown postflight increases of OCR or no changes at all (Clarke and Kornilova 2007; Diamond and Markham 1998; Hofstetter-Degen et al. 1993; Kornilova et al. 2011; Moore et al. 2001; Reschke et al. 1985; Reschke et al. 2018; Vogel and Kass 1986; Young and Sinha 1998). There were some inconsistencies in these results, which may be due to the various experimental procedures employed, including flash afterimages, flash photography of the eyes, and video-oculography, or due to the high variance of the OCR across individuals.

Figure 6 shows the percentage of subjects that demonstrated a significant OCR decrease after spaceflight compared to preflight in each of these studies. The longer the duration of the spaceflight, the higher percentage of subjects showing a postflight OCR decrease, thus indicating that the adaptation of this otolith-mediated reflex takes place throughout the flight (Reschke et al. 2018).

A decrease in static OCR after return from long-duration spaceflight is consistent with the hypothesis that central compensatory mechanisms are activated during prolonged exposure to microgravity for adjusting otolith-mediated responses. On Earth, information from the otolith receptors is interpreted as either linear motion or as head or body tilt with respect to gravity. Because stimulation from gravity is absent during spaceflight, interpretation of otolith input as tilt is meaningless. After several weeks in space, the brain adapts to weightlessness by reinterpreting all otolith receptor output as linear acceleration, and stimulation of the otoliths is interpreted as translation. Immediately after returning from a long spaceflight, and before the CNS readapts to the normal gravity force environment, this new interpretation persists, during which linear acceleration and tilt are both perceived as translation. Consequently, during this post-flight period the otolith-mediated tilt responses, such as the static OCR, are reduced.



Overall results of 11 OCR studies performed before and after spaceflight. Each data point represents the percentage of subjects showing an OCR decrease postflight relative to preflight for the duration of the flight corresponding to that particular study. Study reference and number of subjects tested are indicated next to each data point. Note the logarithmic scale on the x-axis (Flight Duration). The blue line depicts a logarithmic function fitted to the data (r2 = 0.69). (Reschke et al. 2018).

Figure 6. Incidence of post-flight OCR reduction

Eye Movements during Linear Acceleration

Two subjects exposed to transient lateral acceleration 3-5 hours after the landing of the SL-1 mission demonstrated smaller torsional amplitudes than three of the four preflight measures of sinusoidal ocular torsion for these subjects. Torsional amplitude in these subjects steadily increased over most of the post-flight tests, but changes were not statistically significant because of high variability in the preflight measurements (Arrott and Young 1986). Y-axis linear translation enhanced horizontal eye movements in crewmembers 2-3 days after landing (Parker et al. 1986). These results are consistent with the OTTR hypothesis, which predicts reduced eye torsion immediately after landing due to reinterpretation of otolith signals as linear translation (Liao et al. 2011; Parker et al. 1985).

In two recent studies, eye movements and perceived motion were evaluated in astronauts returning from Space Shuttle missions during OVAR (Clément and Wood 2013) and during short-radius centrifugation (Clément and Wood 2014). No changes were seen on the compensatory eye movements to these linear accelerations between pre- and post-flight. However, the crewmembers reported an overestimation of the sensation of roll tilt (but not pitch tilt) and an overestimation of the sensation of translation immediately post-flight. These results confirm that some VORs elicited during passive motion may not be altered by short-duration spaceflight, or may readapt very quickly, and that the resolution of sensory conflict associated with post-flight recovery involves higher-order neural processes (Holly et al. 2010).

Proprioceptive Changes

Overall, the post-flight reports of increased heaviness of static objects suggest that some central rescaling of static pressure systems occurs. A Spacelab D-1 mission required subjects to use higher accelerative shaking forces, which improved their ability to discriminate mass but not weight. Additionally, video recordings of astronauts showed that shaking was faster in-flight compared to preflight and slowed after landing, returning to baseline after three days (Ross et al. 1986a). Error in weight or mass perception may be due to a basic failure of reafference or to inadequate monitoring of command signals and inappropriate scaling of afferent signals.

c. Postural Equilibrium

During the Apollo program post-flight postural ataxia was studied using tandem stance on narrow rails of various widths with eyes either open or closed and arms folded across their chests (Berry and Homick 1973; Homick and Miller 1975; Homick and Reschke 1977; Kenyon and Young 1986). Other studies have used static force plates for stabilometry and simpler tests, such as the clinical Romberg test, a sharpened (toe-to-heel) Romberg test, and vertical posture with varying head positions, to assess postural ataxia immediately after flight (Bryanov et al. 1976; Clément et al. 1984; Yegorov 1979). Other postural performance studies have relied on dynamic posture platforms that translate the subject (Anderson et al. 1986; Clément et al. 1985; Reschke et al. 1984), tilt the subject (Kenyon and Young 1986; Reschke et al. 1991), or provide more sophisticated means of posture control such as stabilization of ankle rotation and/or vision (Paloski et al. 1993). Pre- and post-flight studies of vestibulo-spinal reflexes (Baker et al. 1977; Kozlovskaya et al. 1984; Reschke et al. 1984; Watt et al. 1986) and postural responses to voluntary body movements (Clément et al. 1984; Reschke 1988) have also been performed.

The greatest decrease in stability occurs when subjects must rely on vestibular information alone, when proprioceptive or visual feedback is either altered or absent. Decrements in postural stability with eyes closed are well documented from Skylab missions and were observed to persist for up to 1-2 weeks post-flight (Homick and Reschke 1977). Computerized dynamic posturography (CDP) evaluations conducted after ISS flights clearly demonstrated that postural stability was diminished (Wood et al. 2015). Recovery of postural stability after landing occurs in two phases: initial rapid improvement followed by a gradual recovery. Both the initial decrement and the time required for recovery vary as a function of flight duration. Stability is further compromised during dynamic head tilts (0.33Hz @ ±20° in pitch plane), with a time constant of recovery of 19hr for head erect versus 111hr for head moving, so that the majority of crewmembers are unable to maintain quiet stance for 20 sec. The extent of the postural stability decrement may also reflect previous spaceflight experience (Clark and Bacal 2008). Paloski et al. (Paloski et al. 1993; Paloski et al. 1994; Paloski et al. 1990) initially reported that veteran astronauts seem to have better post-flight postural performance than first-time fliers. However, subsequent analysis of CDP data suggests that there was not consistent improvement over subsequent flights.

A few physiological factors are known to contribute to spaceflight-induced postural instability (Forth et al. 2011). Firstly, the dorsiflexor muscles play a larger role in space than the extensor muscles, which are used to counteract gravity on Earth (Clément et al. 1984). This causes astronauts to assume a forward tilted posture when asked to stand perpendicular to the spacecraft floor. A small flexor tone is generated to maintain the feet at a right angle to the leg, as this is the normal neutral posture of the ankle (Clément and Lestienne 1988). Another explanation for this posture in microgravity is that the normal excitatory drive exerted by input from the otoliths, by way of the vestibular nuclei, on the extensor muscles is inhibited due to the lack of gravity.

Changes in vestibulo-spinal reflexes may also contribute to postural decrements. The Hoffmann reflex and otolith-spinal reflexes were dramatically reduced during space, but differences between pre- and post-flight responses were not significant (Watt et al. 1986). Reschke et al. (1986) observed a potentiation of the Hoffman reflex 40 ms after astronauts underwent an unexpected drop (Earth-vertical fall with bungee cords) during flight; this potentiation disappeared after 7 more days. Immediately after spaceflight, there was significant potentiation again compared to preflight responses. Such changes in the Hoffman reflex are predictive of change in the gain of the spinal reflex pathway. How gain changes in this pathway are linked to preprogrammed muscular activity such as the maintenance of posture is not clear.

d. Locomotion

Locomotor Control and Segmental Activation

Most crewmembers experience some degree of locomotor dysfunction when they return to Earth after spaceflight. Some of these post-flight alterations are ataxia with the sensation of turning while attempting to walk a straight path; sudden loss of postural stability when rounding corners or after unexpected perturbations; and sudden loss of orientation in unstructured visual environments. In addition, some astronauts report oscillopsia (illusory movement of the visual field) while walking.

Foot contact with the ground, the transfer of weight from one foot to the other, and the push-off with the toe from the ground are critical phases, as these interactions with the support surface result in forces that create vibrations, which if unattenuated could interfere with the visual-vestibular sensory systems in the head (Ito and Gresty 1997; Lafortune et al. 1996;

McDonald et al. 1997; Mulavara and Bloomberg 2002; Mulavara et al. 2005a; Pozzo et al. 1990; Smeathers 1989; Voloshin 1988; Whittle 1999). The musculoskeletal system controls these vibrations; muscles and joints act as filters to minimize the perturbing effects of impacts with the ground and help to maintain a stable trajectory at the head (Holt et al. 1995; McDonald et al. 1997). During treadmill walking after returning from long-duration spaceflight, astronauts' knee flexion during the stance phase significantly increased, but it returned to normal within 6–10 days (Mulavara and Bloomberg 2002). An increase in knee flexion during locomotion will result in reduction of the axial stiffness of the lower-limb complex during the critical stance phase following heel strike, leading to reduced perturbations being transmitted to the head during locomotion.

Distinct post-flight performance decrements in gait have been observed in cosmonauts returning from Soyuz missions lasting 2 to 63 days (Bryanov et al. 1976; Chekirda 1970; Chekirda and Eremin 1977). In most cases, the duration of post-flight effects correlated with the duration of the mission. Post-flight changes in locomotion included increased angular amplitude of motion at the knee and ankle and increased vertical accelerations of the center of mass (Hernandez-Korwo et al. 1983).

Post-flight locomotor control and segmental coordination show alterations in muscle activation. Layne et al. (Layne et al. 1998b; Layne et al. 1997) reported that the temporal relationship and relative amplitude of muscle activation are modified by spaceflight, particularly for the events of heel-strike and toe-off that are complementary to evidence of changes in kinematics during locomotion at these events of the gait cycle (McDonald et al. 1996; Miller et al. 2010). The loss of neuromuscular coordination may cause difficulty in achieving optimal transitions between muscles while walking (Courtine et al. 2002). This loss in coordination between muscles may also affect the ability to maintain stable head movement (Layne et al. 2001; Layne et al. 2004) and is complementary to evidence seen in alterations in head-trunk coordination during walking (Bloomberg and Mulavara 2003; Bloomberg et al. 1997; Mulavara et al. 2012); reduced visual acuity during walking (Peters et al. 2011); and impairment in the ability to coordinate effective landing strategies during jump tasks (Courtine and Pozzo 2004; Newman et al. 1997). Other neurophysiological changes including proprioceptive hyper-reactivity, such as increased Hoffman reflex amplitudes; reduced ability to perform graded muscle contractions; and decreased muscle stiffness (Grigor'eva and Kozlovskaya 1987) may also have a contributory influence on muscle coordination during locomotion activity.

Activation of ankle-joint muscles post-flight has been heavily investigated. Zangemeister et al. (Zangemeister et al. 1991) concluded that spaceflight-related adaptive modifications in neural processing of vestibular input could negatively influence activation of lower limbs. This change, in combination with altered strength between ankle plantar flexors and dorsiflexors (Hayes et al. 1992), can cause difficulty in walking.

Changes in ankle musculature activation are suggested to result in reinterpretation of proprioceptive input (Roll et al. 1993). Ankle proprioception is no longer interpreted as coding anterior-posterior body sway while upright but instead codes either whole body axial transportation (i.e., pushing off the support surface) or foot movement exclusively. In addition, the extent of reinterpretation correlates with duration of mission. Despite being appropriate for weightlessness, these changes are maladaptive on return to Earth and may contribute to post-flight decrements in locomotion.

Head-Trunk Coordination

Gaze and head movement control stabilizes vertical and horizontal vision during various motor tasks such as jumping, walking, running, hopping and/or tasks requiring a person to maintain equilibrium on a beam or a moving platform (Assaiante and Amblard 1993; Pozzo et al. 1995). The head serves as a stable platform to provide a veridical reference frame for visual, vestibular, and proprioceptive integration, facilitating the organization of postural and locomotor control patterns (Bloomberg and Mulavara 2003; Bloomberg et al. 1992; MacDougall and Moore 2005; Mulavara and Bloomberg 2002; Pozzo et al. 1990). Another system that benefits from head stabilization with respect to the environment is the system for maintaining gaze during body movement. Head movements actually contribute to gaze stabilization during locomotion (Bloomberg et al. 1992). An example of this is the pitch head rotation (as in nodding the head), which compensates for the vertical translation of the trunk that occurs with each step during the gait cycle. The magnitude of these head rotations was correlated with the distance of the visual target to the eyes. The goal-directed nature of these head movements during concurrent locomotion and visual target fixation suggests that head movements are not completely dependent on passive inertial and viscoelastic properties of the head-neck system but are actively modulated to respond to altered gaze control requirements. Thus, head stabilization mechanisms help adjust posture, maintain balance of the moving body, and maintain visual acuity for navigational control through a constantly varying environment during locomotion.

In an initial study, Bloomberg et al. (Bloomberg et al. 1997) examined whether short-duration exposure (7–16 days) to the microgravity environment of spaceflight during Shuttle missions induces alteration in post-flight head-trunk coordination during locomotion. Before spaceflight, pitch head movements acted in a compensatory fashion to oppose vertical trunk translation during locomotion. As the trunk translated upward, the head pitched forward and downward, assisting in maintaining target fixation. Following spaceflight, coordination between compensatory pitch angular head movements and vertical trunk translation was significantly altered. Like with vestibular deficits (Keshner and AK 1994; Keshner et al. 1995; Lawson et al. 2016) and children prior to development of their mature head stabilization response (Assaiante and Amblard 1993), head movements were restricted during locomotion. This change in head-trunk coordination strategy may account, in part, for the reported oscillopsia that occurs during post-flight locomotion and may contribute to disruption in descending control of locomotor function. Comparison of responses from multi- and first-time astronauts indicated that astronauts who had experienced more than one spaceflight demonstrated less post-flight alteration in the frequency spectra of pitch head movements than subjects on their first flights.

Changes in head-trunk coordination during locomotion were also characterized in returning Mir crewmembers (Bloomberg and Mulavara 2003). These subjects walked (6.4 km/h) on a treadmill before and after spaceflight while visually fixating on an earth-fixed target. At this walking speed, head pitch movements compensate for the vertical trunk movements that occur during each step (Bloomberg et al. 1997; Pozzo et al. 1990; Pozzo et al. 1995). Subjects showed a reduction in head movements in the frequency range of 1.5-2.5 Hz, reflecting the contributions of reflexive head stabilization mechanisms (Keshner et al. 1995) during post-flight locomotion followed by a recovery trend spanning several days. This reduction in head pitch movement occurred despite no significant change in trunk pitch or vertical movement. Therefore, during post-flight locomotion head movement amplitude with respect to space was reduced.

Bloomberg et al. (Bloomberg et al. 1997), Davids et al. (Davids et al. 2003), Mulavara et al. (Mulavara et al. 2005b) and Madansingh and Bloomberg (Madansingh and Bloomberg 2015) have shown that tasks requiring sensorimotor integration after an adaptive exposure are associated with a wide range of adaptive behavioral responses. Specifically, after short-duration spaceflight, astronauts showed diverse responses, with some showing increases and others showing decreases in the magnitude of head pitch movement during walking (Bloomberg et al. 1997). A report from Mulavara et al. (Mulavara et al. 2012) confirms and extends this observation of response variability one day after return from long-duration spaceflight on board the ISS. Subjects were classified into two groups according to the pre- and post-flight averages of the magnitude of their head pitch movements during locomotion: a “decreaser” group wherein subjects’ post-flight average head pitch movements decreased with respect to their preflight average, and an “increaser” group, wherein subjects’ post-flight average exceeded their preflight average. The vertical torso translation was not significantly different after exposure to spaceflight compared to preflight.

Zangemeister et al. (Zangemeister et al. 1991) demonstrated that normal locomotion performed with the head in a retroflexed position induces alterations in lower limb muscle activity patterns. They concluded that a functional linkage exists between otolith signals generated by various head positions and the muscle activity patterns generated in the lower limbs during locomotion. Appropriate attenuation of energy transmission during locomotion, achieved by the lower limbs’ joint configuration coupled with appropriate eye-head-trunk coordination strategies, was demonstrated as being a fundamental feature of an integrated gaze-stabilization system during locomotion (Bloomberg and Mulavara 2003; Mulavara and Bloomberg 2002; Mulavara et al. 2005a). From this point of view, the whole body is an integrated gaze-stabilization system to which several subsystems contribute, leading to accurate visual acuity during body motion. Given these functional linkages, it can be argued that spaceflight induces adaptive modification in segmental coordination and disrupts coordinated body movement during post-flight terrestrial locomotion. It follows that active body movement in the unique inertial environment encountered during spaceflight may require subjects to adaptively acquire novel head-trunk and lower body segmental control strategies. Adaptation to long-duration spaceflight leads to modified head stabilization mechanisms; modified transmission characteristics of the shock wave at heel strike; and increased total knee movement during the subsequent stance phase during post-flight walking. These strategies, however, may be maladaptive for locomotion in a terrestrial 1 g environment leading to impairment of locomotor function during the readaptation period following the return to Earth.

Previous spaceflight data have shown post-flight increases in vestibulo-spinal reflexes in humans and increased utricular afferent sensitivity to translation shown in toadfish (Boyle et al. 2001; Reschke et al. 1984). Upregulation of the sensitivity of the utricular afferents after adaptation to 0 g may be manifested in the "increaser" group of astronaut subjects. However, a similar increase in vestibular sensitivity would tend to generate larger head pitch for the same trunk vertical translation during locomotion (Moore et al. 2006). A similar increase in head movements in the pitch direction was observed in all subjects who had undergone 30 minutes of adaptation to locomotion while unloaded to 60% of body weight with no changes in trunk vertical translation during locomotion (Mulavara et al. 2012). This was not the case for the subjects in the "decreaser" group of astronaut subjects. Data from experiments with labyrinthine-deficient patients and experiments in which galvanic vestibular stimulation (GVS) was used to induce acute vestibular disturbances indicated that a reduction in head movement response could be a voluntary strategic response to reduce sensory conflict (Mulavara et al. 2012). Thus, the "decreaser" group of subjects may show an increased weighting of vestibular signals, hence sensory weighting may be a marker of post-flight disturbance. This strategy may also reflect the response of a control system looking for a new equilibrium point. The goal of establishing this new end point would be to reduce potential canal-otolith ambiguities.

The lack of change in vertical trunk translation indicates that the input disturbances to the gaze control system remain unchanged. Taken together, the kinematic and gaze stabilization findings indicate that body load-sensing somatosensory input centrally modulates vestibular input and can adaptively modify vestibularly mediated head-movement control during locomotion. Thus, spaceflight may cause a central adaptation of the converging vestibular system and the body load-sensing somatosensory system, leading to alterations in head-movement control.

Dynamic Visual Acuity

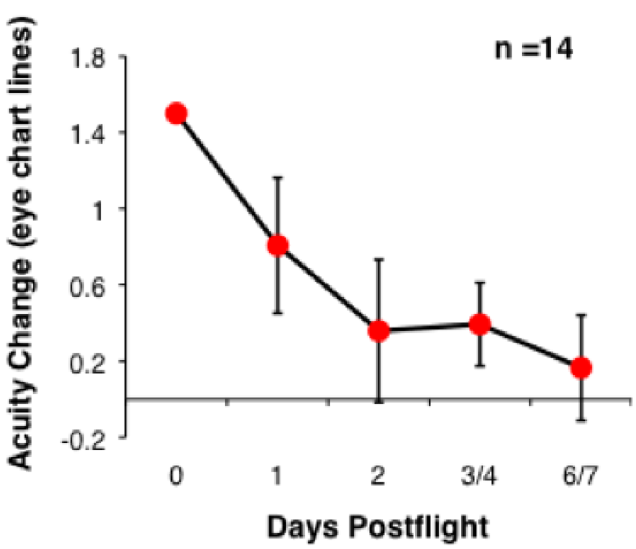
Gaze control orchestrated by the CNS is critical to dynamic visual acuity (DVA), the ability to see an object clearly when the object, the observer, or both are moving. Deficient gaze control experienced following G-transitions causes oscillopsia, or blurred vision, and decrements in dynamic visual acuity, with stationary objects appearing to bounce up and down or move back and forth during head movements. Decreased dynamic visual acuity caused by spaceflight can lead to misperception of sensory information and poses a unique set of problems for crewmembers, especially during entry, approach, and landing on planetary surfaces. Visual disturbances could adversely affect entry and landing task performance, such as reading instruments, locating switches on a control panel, or evacuating a vehicle in suboptimal visual conditions (e.g., smoke in the cabin). Post-flight oscillopsia and decreased dynamic visual acuity could decrease crewmember safety when returning to normal duties (e.g., driving a rover, scuba diving, or piloting an aircraft) or activities of daily living (e.g., driving, contact sports, climbing ladders, etc.) after flight.

Measures of dynamic visual acuity (DVA) have been used as a diagnostic tool for identifying vestibular dysfunction (Hillman et al. 1999; Lee et al. 1997; Schubert et al. 2001; Schubert et al. 2002; Tian et al. 2001). However, even persons with healthy vestibular function can experience, under certain conditions, compromised visual performance (Deshpande et al. 2013). Human factors (i.e. ergonomics) investigations looking at the effects of whole-body vibration have documented changes in visual performance over a wide range of stimulus conditions (Boff and Lincoln 1988; Demer and Amjadi 1993; Griffin 1990; Meddick and Griffin

1976; Moseley and Griffin 1986). An important factor for determining the visual performance in these investigations is the transmissibility of the vibration to the head. Factors such as the subject's posture and muscle tone, as well as their coupling to contact surfaces or added masses, can have an effect on visual performance. The coupling between astronauts and their spacecraft during critical phases of the mission (e.g., entry, landing) could therefore affect their ability to see clearly.

McDonald et al. (McDonald et al. 1997) discussed the implications to gaze control of adaptive changes in musculoskeletal impedance and posture after spaceflight. Musculo-skeletal impedance is also affected by G-loading, which in turn affects vibration sensitivity; G- and vibration-loading often occur together during launch and entry/landing. Visual performance may well be degraded while standing during piloting, as potentially proposed for future planned spaceflight missions and previously employed during the Apollo program.

Decreased DVA performance was demonstrated in astronauts following return from long-duration spaceflight (Bloomberg and Mulavara 2003; Peters et al. 2011). A second-generation test using Landolt C characters instead of numbers also documented decrements in DVA performance as a function of time after flight in crewmembers returning from long-duration space missions (Peters et al. 2011) (Figure 7). For some subjects the decrement was greater than the mean acuity decrement seen in a population of vestibular impaired collected using a similar protocol (Lawson et al. 2016). The population mean showed a consistent improvement in DVA performance during the two-week post-flight recovery period. These results may significantly underestimate the decrements in visual performance that are actually experienced during and immediately following landing because all DVA data (with the exception of one subject) were collected no earlier than 24 hours after landing. Given how rapidly VOR function and gaze control re-adapts the decrement in visual acuity at the actual time of landing was likely much higher than measured during the first postflight data collection session.



Dynamic visual acuity data during treadmill walking from 14 crewmembers after return from 6-month ISS flights. Data are normalized to the subjects' preflight DVA values, which are represented on the y-axis at 0. These data show a decrement in postflight walking acuity followed by an improvement in performance during the postflight recovery period (from Peters et al, 2011).

Figure 7. Post-flight DVA Recovery

Changes in dynamic visual acuity also contribute to functional changes (on the ground) in patients with vestibular disorders (Herdman 1994). For various reasons, physicians often caution patients with vestibular disorders against driving (Cohen et al. 2003). Clark & Rupert (Clark and Rupert 1992) report on a case study involving a student naval aviator with a similar complaint. Turbulence caused the aviator to become unable to see the instrument panel clearly. Testing revealed that the student had defective VOR function. As a result, his eye movements were not able to compensate adequately for the motions of his body in turbulent conditions.

Jump Performance

Following spaceflight, crewmembers also experience changes in the otolith-spinal reflex mechanisms that are essential for the preprogrammed motor strategies used for impact absorption after a jump. Watt et al. (Watt et al. 1986) tested Shuttle astronauts during sudden "drops" and reported that all subjects were unsteady post-flight. The otolith-spinal reflex, which helps prepare the leg musculature for impact in response to sudden falls, is dramatically reduced during spaceflight. Reschke et al. (Reschke et al. 1986) used the Hoffman-reflex to examine the effect of drops on the sensitivity of the lumbosacral motoneuron pool, which is presumably set by descending otolith control signals. A large potentiation of the Hoffman-reflex recorded in the soleus muscle was found beginning approximately 40 ms following an unexpected drop. This potentiation of the Hoffman reflex during drops vanished on the 7th day of spaceflight. Immediately following spaceflight, two of four subjects demonstrated a significant increase in potentiation during the drop compared with pre-flight testing.

Shuttle astronauts were also tested pre-flight and post-flight (< 4 hr after return) on voluntary 2-footed downward hops from a 30 cm high step. Motion analysis of the jump indicated impairment in the ability to coordinate effective landing strategies (Courtine and Pozzo 2004; Newman et al. 1997). A decrease in hip flexion and changes in the center of mass position relative to the feet were observed. The majority of crewmembers fell backwards (likely due to a potentiated stretch reflex) on the first of three jumps, and there was a greater use of arms for balance. These data provide further evidence for post-flight changes in motor programming during the jump aerial phase and impaired ability to prepare the limb muscles for the impact phase of the jump.

Other work indicates that spaceflight may affect proprioception of limb position. Watt (Watt 1997) found a considerable decline in arm-pointing accuracy while blindfolded during and immediately following spaceflight. When they performed deep rhythmic knee and arm bends after spaceflight, subjects reported that floors and walls moved toward them, and that their knees bent more rapidly than intended. This can be partly explained by an abnormal level of muscle spindle receptor activation on return to 1 g, which results in misinterpretation of muscle length and subsequent abnormal flexion. Therefore, altered jumping performance seen post-flight may reflect decrements in limb proprioception sense, combined with altered central interpretation of otolith acceleration cues and vestibulo-spinal reflexes.

e. Functional Performance Measures

Functional Mobility

Pre- and postflight functional mobility assessment was performed on ISS crewmembers to determine their ability to complete challenging locomotor maneuvers similar to those encountered during an egress from a space vehicle (Mulavara et al. 2010). To perform the Functional Mobility Test (FMT) subjects walked at a self-selected pace through an obstacle course set up on a base of medium density foam that increased the challenge of the test. There was a 48% increase in time to traverse the course one day after landing, and recovery of function took an average of 15 days to return to within 95% of their preflight level of performance (Figure 8).

The results also showed that post-flight recovery can be divided into two processes: rapid strategic learning over the six trials on the first day after return, and a slower process taking over 2 weeks to recover to a pre-flight level of performance. It is believed that training can promote or enable these strategic or early learning responses for facilitating faster re-adaptation to Earth’s 1-g environment on return from spaceflight. Additionally, a significant positive correlation between measures of long-term recovery and early motor learning (strategic learning) indicates that the two types of recovery processes influence an astronaut’s ability to re-adapt to Earth’s gravity environment. Early motor learning helps astronauts make rapid modifications in their motor control strategies during the first hours after landing. Further, this early motor learning appears to reinforce the adaptive realignment, facilitating re-adaptation to Earth’s 1-g environment on return from spaceflight.

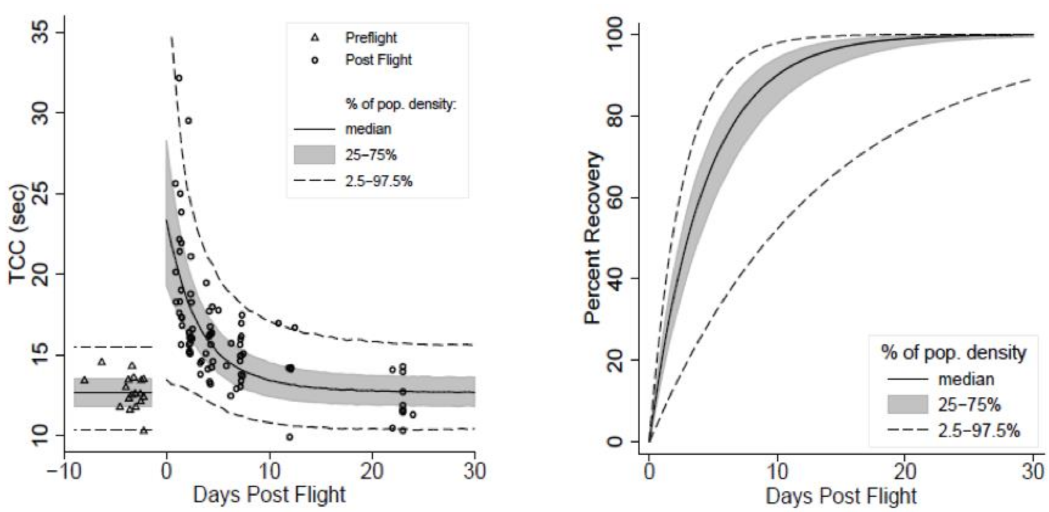


Figure 8. Post-flight FMT recovery

Left: Scatter plot of time to complete the course (TCC) for 18 long-duration subjects showing a 48% increase in time to traverse the obstacle course one day after landing. Right: Recovery of function took an average of 15 days to return to within 95% of their preflight level of performance.

Adaptation to different gravitational environments may affect planetary extravehicular activities during the initial adaptation period due to postural and locomotor dysfunction. These alterations may also lead to decrement in the ability to multi-task along with increasing the metabolic costs of ambulation. A recent study examined subjects walking on a destabilizing support surface using a treadmill mounted on a six-degree-of-freedom motion base that provided an oscillating support-surface during walking (Peters et al. 2013). Results demonstrated that measures of locomotor stability, cognitive load, and metabolic cost were all significantly greater during support-surface motion than during baseline walking conditions and showed a trend toward recovery to baseline levels during locomotor adaptation. These decrements are operationally meaningful because they indicate broader functional implications for postflight locomotor instability (Brady et al. 2012; Brady et al. 2009). Until recently, locomotor adaption to discordant sensory conditions has been characterized primarily in terms of impact on the underlying mechanisms contributing to locomotor stability. These results indicate that uncoordinated walking during periods of adaptive change may also come at significant cognitive and metabolic costs to the crew. Cognitive load increases and metabolic cost rises because of new demands on attention and additional physical work required to maintain balance while walking. Energetic cost is a key contributor to the duration and intensity of EVAs performed by suited astronauts, and previous research on suited locomotion has explored the effects of load, slope, and walking vs. running (Carr and Newman 2007a; Carr and Newman 2007b). Metabolic cost associated with locomotor instability is a factor that should be accounted for in the continuing efforts to improve extravehicular suit design.

Functional Task Tasks

To understand how changes in physiological function affect functional performance, an interdisciplinary pre- and post-flight testing regimen, Functional Task Test (FTT), was developed to systematically evaluate both astronaut functional performance and related physiological changes (Arzeno et al. 2013; Bloomberg et al. 2015a; Ryder et al. 2013; Spiering et al. 2011). Ultimately this information will be used to assess performance risks and inform the design of countermeasures for exploration class missions. This FTT study was conducted on Shuttle and ISS crewmembers before and after 6-month expeditions and is currently being conducted for 1-year expeditions. Additionally, in a corresponding study, the FTT protocol was used on subjects before and after 70 days of 6° head-down bed-rest as an analog for spaceflight. Bed-rest provides the opportunity to investigate the role of prolonged axial body unloading in isolation from the other physiological effects produced by exposure to microgravity (Reschke et al. 2009). Therefore, the bed-rest analog allowed the investigation of the impact of body unloading on both functional tasks and on the underlying physiological factors that lead to decrements in performance, subsequently allowing comparison of those with results obtained after spaceflight.

Functional tests included ladder climbing, hatch opening, jump down, manual manipulation of objects and tool use, seat egress and obstacle avoidance, recovery from a fall, and object translation tasks (Bloomberg et al. 2015a). Physiological measures included assessments of postural and gait control, dynamic visual acuity, fine motor control, plasma volume, heart rate, blood pressure, orthostatic intolerance, upper- and lower-body muscle strength, power, endurance, control, and neuromuscular drive. ISS crewmembers were tested three times before flight, and 1, 6, and 30 days after landing. Subjects in bed rest studies were tested three times before bed rest and immediately after getting up from bed rest as well as 1, 6, and 12 days after reambulation.

Astronaut data showed that functional tests requiring a greater demand for dynamic control of postural equilibrium (i.e., fall recovery, seat egress and obstacle avoidance during walking, object translation, jump down) showed the greatest decrements in performance (Bloomberg et al. 2015a). Functional tests with reduced requirements for dynamic postural stability (i.e., hatch opening, ladder climb, manual manipulation of objects and tool use) showed less reduction in performance. Similarly, subjects exposed to prolonged bed rest (> 20 days) showed the same trends in performance change as astronauts, namely a reduction in performance on functional tests requiring a greater demand for dynamic control of postural equilibrium. For both spaceflight and bed rest subjects, these changes in functional performance were paralleled by similar decrements in physiological tests designed to specifically assess postural equilibrium and dynamic gait control (Miller et al. 2018; Mulavara et al. 2018).

Taken together, the spaceflight and bed rest results indicate that the unloading of body support structures (major postural muscles) that is experienced during spaceflight plays a central role in post-flight alteration of functional task performance and balance control. In addition, these data point to the importance of providing significant axial body loading during in-flight treadmill and resistive exercise. Although the body loading and exercise stimulus provided by current resistive and aerobic exercise protocols are critical for maintaining muscular and cardiovascular functions and accelerating sensorimotor recovery, the do not fully protect against balance decrements immediately after spaceflight or spaceflight analogs (Miller et al. 2018; Mulavara et al. 2018). These data indicate that balance training should be used to supplement current in-flight aerobic and resistive exercise activities.

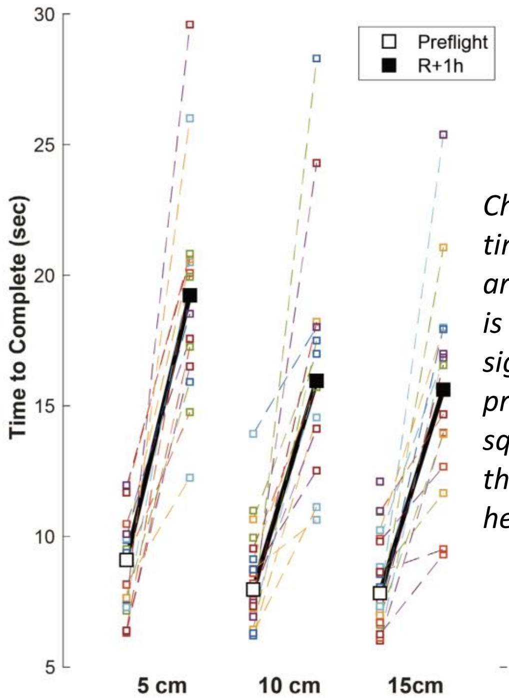
Field Tests

Testing of crew responses following long-duration flights has not been previously possible until a minimum of +24 hours after landing. As a result, it has not been possible to determine the trend of the early recovery process, nor has it been possible to accurately assess the full impact of the decrements associated with long-duration flight. To overcome these limitations, both the Russian and U.S. programs have implemented joint testing at the Soyuz landing site. This ISS research effort has been identified as the Field Test and represents data collected on NASA United States Orbital Segment (USOS) and Russian crews (Reschke et al. 2020a).

The primary goal of this research is to determine functional abilities associated with long-duration spaceflight crews beginning as soon after landing as possible on the day of landing (typically within 1 to 1.5 hr). This goal has both sensorimotor and cardiovascular elements. To date, the NASA and Russian teams collected data on a total of 39 different USOS and Russian crewmembers in both the pilot and full Field Test, with 9 Russian crewmembers being tested twice (total of 48 subject assignments). The study assessed functional sensorimotor measurements including hand/eye coordination, standing from a seated position (sit-to-stand), walking normally without falling, the measurement of dynamic visual acuity, discriminating different forces generated with the hands (both strength and ability to judge slight differences of force), standing from a prone position, coordinated walking involving tandem heel-to-toe placement (tested with eyes both closed and open), walking normally while avoiding obstacles of differing heights, and determining postural ataxia while standing (measurement of quiet stance). A number of these tests have been utilized and tested for sensitivity and specificity in a relatively large cohort of normal and clinical patient populations (Cohen et al. 2012a; Cohen et al. 2012b; Cohen et al. 2014; Cohen et al. 2013; Lawson et al. 2016; Miller et al. 2018; Mulavara et al. 2013; Mulavara et al. 2018; Peters et al. 2013; Peters et al. 2012b).

Sensorimotor performance has been obtained using video records and data from body worn inertial sensors. The cardiovascular portion of the investigation has measured blood pressure and heart rate during a timed stand test in conjunction with postural ataxia testing (quiet stance sway) as well as cardiovascular responses during sensorimotor testing on all of the above measures. Motion sickness data associated with each of the postflight tests has also been collected. When possible, a rudimentary cerebellar assessment was undertaken. In addition to the immediate postlanding collection of data, postflight data has been acquired twice more within 24 hours after landing, and measurements continue until sensorimotor and cardiovascular responses have returned to preflight normative values (approximately 60 days postflight).

The level of functional deficit observed in the crew tested to date is more severe than expected, clearly triggered by the return to gravity loads immediately after landing when the demands for crew intervention in response to emergency operations were greatest (Reschke et al. 2020a). For example, time to complete a seat egress and walking task that involved turning 180 degrees and stepping over obstacles significantly increased on landing day (Figure 9). Measurable performance parameters – such as ability to perform a seat egress, recover from a fall or the ability to see clearly when walking, and related physiologic data (e.g., orthostatic responses) – are required to provide an evidence base for characterizing programmatic risks and demonstrate the degree of variability among crewmembers for exploration missions where the crew will be unassisted after landing. Overall, these early functional and related physiologic measurements will allow the estimation of nonlinear sensorimotor and cardiovascular recovery trends that have not been previously captured (Reschke et al. 2015).



Changes in the Walk and Turn with Obstacle time to completion in sec. Individual responses are shown with dashed lines while the solid line is the mean response. The completion time significantly increased ($p < 0.01$) between preflight (open square) and landing day (closed square) for all three obstacle height trials. Note that these were performed in order of increasing height (5 cm first).

Figure 9. Field Tests Walk and Turn with Obstacle

Navigation

To quantify performance in orienting during free walking after spaceflight, astronaut subjects were asked to walk, preflight and post-flight, a previously seen triangular path with normal vision and vision occluded (Glasauer et al. 1995). The path, marked on the ground by a cross at each corner, consisted of a right triangle with two legs 3-m long. The trajectories of three infrared-reflective markers fixed on a helmet were recorded using a video-based motion analysis system. Subjects showed inter-individual differences, especially for directional deviations from the path, in the vision-occluded condition even preflight; the characteristics of these differences persisted throughout all experimental sessions. The absolute directional errors turned out to be larger post-flight, which means that subjects had larger directional errors but in different directions. In the post-flight condition, however, there was a trend to a larger underestimation of the angle turned at each corner. In contrast to directional errors, the length of the legs walked was similar pre- and post-flight. These data suggest that the perception of self-displacement during turning, but not during linear motion, was changed by the stay in weightlessness. A possible explanation could be the development of a mismatch between information from otoliths and semicircular canals during whole-body turns in microgravity. This change in canal-otolith interaction may underlie the disturbances in locomotion experienced by returning astronauts.

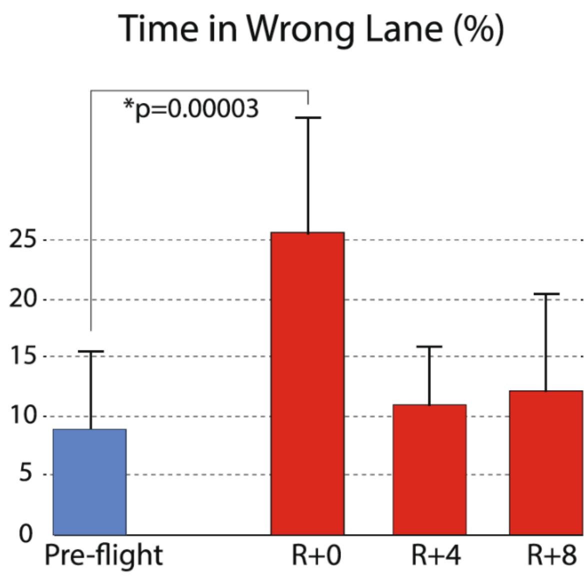
f. Manual Control

Beginning with STS-80, returning Shuttle crews have been examined by flight surgeons for neurologic dysfunction within several hours of landing. Commanders were scored for subjective symptoms, coordination, and functional motor performance. Data analyzed from nine missions noted trends, such as an apparent correlation between down range touchdown, sink rate, and difficulty arising from a chair without using the arms (McCluskey et al. 2001). Generally, scores indicative of neurovestibular dysfunction correlated with flying a lower approach and landing shorter or longer, faster, and harder. When plotted as a function of generalized gaze problems observed by the flight surgeons, there were only four landings within the optimal range on the runway. When gaze was judged as severely affected, the landings were clearly short of the desired touchdown point. These observations suggest that further analysis of Shuttle landing performance is warranted.

In studies performed immediately after two Spacelab missions, returning astronauts were seated on a rail-mounted sled and asked to use a joystick to null a random linear disturbance movement along their interaural (Arrott and Young 1986) and/or longitudinal (Merfeld et al. 1996) body axes. Four of the seven subjects tested showed improved post-flight performance on the nulling task. Also, Merfeld et al. (Merfeld 1996) tested the early post-flight performance of astronauts trying to maintain a flight simulator in an upright orientation in the presence of pseudorandom motion disturbances about a tilt axis located below their seat. On landing day, both subjects showed impaired ability to control their tilt in the dark but displayed normal responses when visual motion cues were provided. Results confirm that returning crews have difficulty estimating their tilt orientation with respect to the gravitational vertical on landing day. The absence of change with visual cues shows that neuromuscular and fatigue factors were not major contributors to the effect. It is important to note that the subjects in these experiments all knew whether tilt or translation motions were possible. Subsequent ground-based experiments (Park et al. 2006; Wertheim et al. 2001) showed that when subjects must resolve tilt-translation ambiguities, and are naïve to the possible motion, large misperceptions of tilt could result.

A study of visual-manual tracking before and after spaceflight ranging from 159 to 195 days involving 14 cosmonauts was performed by Kornilova et al. (Kornilova et al. 2016). Results showed that performance of tracking visual targets moving at 0.16 Hz (± 10 deg) significantly decreased after the flight. This decrease was less pronounced for the manual tracking. Both visual and manual tracking returned to baseline on R+8.

Another study used three full-motion simulations (driving a car, piloting a T38 jet, and navigation and docking of a Mars rover study) to determine the impact of long-duration spaceflight (mean 171 days) on post-landing operator proficiency in eight astronauts (Moore et al. 2019). While there were no significant pre- versus post-flight differences during a T-38 simulation, there was an increase in variability in several key parameters. For example, the touchdown force standard deviation increased from 2,648 lbs (range 5,048 – 14,283 lbs) pre-flight to 4,205 lbs (range 710 – 15,143 lbs) post-flight. The T-38 overhead approach was chosen because of the low-frequency banking turns required to circle the runway while maintaining altitude and airspeed until the final approach. This post-ISS study observed significant errors in tilt perception at lower frequencies (0.12 Hz) on the initial testing that recovered within 4 days (Moore et al. 2019). There were also significant deficits in post-landing driving performances during a winding road simulation, including increases in lane crossings, time to recover and time spent in the wrong lane (Moore et al. 2019). There was also increased variance in docking alignment on the rover task (Wood and Moore 2017). These deficits were not primarily due to fatigue, since performance on the same tasks was unaffected in a ground control study after a 30-h period of sleep restriction. These vehicle simulation studies raise concerns that astronauts will face increased post-flight risk of operational task failure. Other laboratory-based measures support the finding that spaceflight markedly impairs fine motor control, including force modulation (Rafiq et al. 2006), surgical operating completion time (Campbell et al. 2005), keyed pegboard completion time (Mulavara et al. 2018), and bimanual coordination (Tays et al. 2021).



Post-flight performance following ISS missions on a 3 km mountain driving simulation manifested a number of deficits, including the % time in the wrong lane pictured her (from Moore et al, 2019).

Figure 10. Driving simulation performance following ISS

g. Impact of Vestibular Changes to Orthostatic Intolerance

The vestibular system is required for motion sickness to occur, but the exact neural pathways involved are still unknown. Understanding the role of the vestibular system in autonomic regulation is essential to understanding SMS (Davis et al. 1993a; Davis et al. 1988). Some authors argue that unusual motion or direct vestibular stimulation triggers a poison response (Money 1996). The poison response consists of a stress response and stomach emptying. Vomiting is primarily associated with increases in parasympathetic activity, whereas stress responses are primarily associated with increases in sympathetic activity or decreases in parasympathetic activity (or both). The most direct pathway for vestibular modulation of autonomic responses involved in motion sickness is efferent projections from the medial and inferior vestibular nuclei to the nucleus tractus solitarius (NTS) in the brainstem and the dorsal motor nucleus of the vagus. The NTS plays an integral role in both gastric motility and emesis related to motion sickness (Ito and Honjo 1990). The NTS receives input from peripheral and central ascending fibers (Barron 1993; Onai et al. 1987) and in turn influences vagal stimulation of the stomach and heart and activation of the sympathetic nervous system (Previc 1993; Yates 1992; Yates et al. 1993; Yates and Miller 1996). The cerebellum may be another route through which vestibular inputs may modulate autonomic activity (Balaban 1996; Wood et al. 1994).

Stimulation of the vestibular system can influence behavioral responses by regulating several higher centers in the central and autonomic nervous system (Rajagopalan et al. 2017). The vestibular system modulates vegetative functions via ascending and descending pathways, e.g., from the vestibular nuclei to the locus coeruleus, the amygdala, the limbic cortex, and the hypothalamus (Balaban 2004). Notably, the amygdala is involved in the development of and habituation to motion sickness (Nakagawa et al. 2003).

Clinical and physiological evidence suggests that the vestibular system participates in autonomic control by stimulating the vagal system and inhibiting the sympathetic system (Holstein et al. 2014; Yates and Bronstein 2005). Emerging evidence suggests that the vestibular system helps protect against presyncope (e.g., lightheadedness, dizziness) and syncope (fainting) by detecting head movements and evoking the vestibulo-sympathetic reflex. When the body maneuvers into an upright stance the cardiovascular system must respond rapidly to minimize pooling of blood in the lower body, to protect venous return and stroke volume, and to maintain blood supply to the brain. The vestibulo-sympathetic reflex operates during orthostatically challenging movements to initiate cardiovascular responses in advance of a baroreceptor-mediated response. Recent studies have shown an association between changes in vestibular function and cardiovascular responses during a prone-to-stand movement in astronauts after return from long-duration spaceflight (Deshpande et al. 2020; Hallgren et al. 2015). These results indicate that an appropriate vestibular function is important to evoke optimum vestibulo-sympathetic response during orthostatically challenging, voluntary movements performed after spaceflight.

There is substantial evidence that, even after short periods of microgravity, a sudden rise to an upright position can result in an episode of orthostatic intolerance, i.e., fainting (Hargens and Watenpaugh 1996). This post-spaceflight orthostatic intolerance (PSOI) could be viewed as a functional deficiency following spaceflight. However, Edgerton & Roy (Edgerton and Roy 2000) argue that this response helps to maintain adequate blood flow to the head by assuring that the person does not remain in an upright position when there is a critical cardiovascular challenge that limits blood flow to the brain. This is a classic example of coordination between neural control of the distribution of blood in varying gravitational environments with neural control of skeletal muscles. In this case, neural mechanisms of the cardiovascular system take complete control of the motor systems by rapidly inhibiting those skeletal muscles that maintain an individual in an upright position.

Historically, factors that have been thought to contribute to PSOI include spaceflight-related volume depletion (Bungo et al. 1985; Charles and Lathers 1991; Fischer et al. 1967; Johnson et al. 1977) and excessive venous pooling in the lower extremities (Buckey et al. 1992; Johnson et al. 1976) or splanchnic circulation. Later findings, however, suggest that abnormalities in autonomic cardiovascular control, including a loss of carotid-cardiac baroreflex range and slope during and after spaceflight (Fritsch et al. 1992; Fritsch-Yelle et al. 1994) and a deficit in peripheral vasoconstriction in the upright position on landing day may play a primary role in PSOI (Buckey et al. 1996; Fritsch-Yelle et al. 1996). These autonomic factors were reemphasized given the finding that little correlation exists between deficits in plasma volume and deficits in orthostatic tolerance in returning astronauts. There is evidence that vestibular signals can influence sympathetic outflow. (Convertino et al. 1997; Doba and Reis 1974;

Essandoh et al. 1988; Gillingham et al. 1977; Ray et al. 1997; Satake et al. 1991; Serrador et al. 2009a; Serrador et al. 2009b; Shortt and Ray 1997; Woodring et al. 1997; Yates 1992; Yates and Kerman 1998). The neuroanatomic and neurophysiologic bases for vestibular contributions to autonomic cardiovascular control were reviewed thoroughly by Yates and colleagues (Yates 1992; Yates 1998; Yates and Kerman 1998; Yates and Miller 1996; Yates and Miller 1998; Yates et al. 1998).

The following, taken together, provide strong evidence that changes in vestibular (and especially otolith) function during spaceflight contribute to PSOI: (1) changes in otolith function (Vogel and Kass 1986; Young et al. 1986) and structure (Ross 1993; Ross 1994) have been described and verified in multiple studies during and after spaceflight; (2) signals from intact otolith organs clearly contribute to sympathetically mediated peripheral vasoconstriction in animals (Doba and Reis 1974; Woodring et al. 1997; Yates 1992; Yates 1998; Yates and Kerman 1998; Yates and Miller 1998) and likely contribute to sympathetically mediated peripheral vasoconstriction in humans (Essandoh et al. 1988; Normand et al. 1997; Ray et al. 1997; Shortt and Ray 1997); and (3) the key autonomic defect associated with PSOI in most returning crewmembers is inadequate sympathetically mediated peripheral vasoconstriction (Buckey et al. 1996; Fritsch-Yelle et al. 1996). In spite of all this evidence, however, the precise role of vestibular-autonomic factors in PSOI remains to be defined. Further ground-based studies using both labyrinthine-deficient and -intact humans and animals will be required before any definitive treatment or prophylactic regimens can be designed based on an assumption of underlying vestibular-autonomic pathology. Ultimately, PSOI could be viewed as a functional deficiency following spaceflight.

h. Effect of Spaceflight on the Brain

Human and animal work has revealed both negative and positive effects of spaceflight and spaceflight analogs on the central nervous system. Potential negative effects include changes in cerebral blood flow and alterations to brain structure, including evidence for an upward shift of the brain within the skull and disrupted white matter structural connectivity. Retrospective analysis of long duration crewmembers has demonstrated changes in diffusion tensor metrics and volumetric measures in brain regions involved in the visual function (Riascos et al. 2019). Potential positive effects include increased motor cortical excitability and structural and functional plasticity, suggestive of sensory reweighting processes with spaceflight. Thus, similar to the behavioral changes that occur, it appears that two broad categories of central nervous system changes occur with spaceflight: (a) structural and functional central nervous system dysfunctions, and (b) adaptive plasticity and sensory reweighting. Examination of these central nervous system changes in conjunction with behavioral changes can help to clarify whether these effects represent impairments versus adaptations (Hupfeld et al. 2020).

Fluids and Brain Positional Shift

A single-subject case study revealed some evidence for dysfunction after six months of flight, including decreased motor and vestibular network connectivity, paired with vestibular ataxia and motor coordination declines (Demertzi et al. 2016). Other studies showed an upward shift of the brain within the skull, accompanied by reduced gray matter volume in inferior and frontal brain regions, and increases in superior and posterior regions (Koppelmans et al. 2016). These changes were found to be larger in individuals who had spent six months on the ISS than in those who spent just a few weeks on a space shuttle mission. With additional analyses on the same dataset, Roberts et al. (Roberts et al. 2017) reported narrowing of the central sulcus, increases in ventricular width and volume, and upward displacement of the cerebellar tonsils. In combination, these findings suggest compression of adjacent venous structures and impedance of cerebral spinal outflow. Lee et al. (Lee et al. 2019b) also reported increased free water at the base of the cerebrum and decreases along the posterior vertex, due to mechanical displacements of fluid due to microgravity.

Crewmembers showed reduced fractional anisotropy, a measure of myelin integrity, in white matter structures implicated in vestibular function, visuospatial processing, and sensorimotor control, namely superior and inferior longitudinal fasciculi, inferior fronto-occipital fasciculus, corticospinal tract, and the cerebellar peduncles (Lee et al. 2019b). These changes indicate disrupted white matter structural connectivity, which may negatively impact multi-sensory integration and motor behavior. Consistent with this idea, crewmembers exhibiting greater post-flight disruptions in white matter structural connectivity in the superior longitudinal fasciculus showed greater declines in balance from pre- to post-flight (Lee et al. 2019b).

It is not yet clear how these fluid and brain positional shifts resolve over time upon return to Earth, how they affect health, or how they impact astronaut functional performance (Roy-O'Reilly et al. 2021). These shifts are potentially related to spaceflight associated neuro-ocular syndrome, or SANS (Lee et al. 2020a). This syndrome describes ocular structural changes that have been reported in approximately one third of long duration astronauts, including flattening of the back of the globe, optic disc edema, optic nerve kinking and choroidal folding (Huang et al. 2019; Lee et al. 2017; Mader et al. 2013; Taibbi et al. 2013). For example, Alperin & Bagci (Alperin and Bagci 2018) found that greater post-flight globe deformation in astronauts was associated with increases in ventricular and orbital CSF volumes. Similarly, Van Ombergen et al. (Van Ombergen et al. 2019) reported increases in CSF volume within the lateral and third ventricles following spaceflight, and post-flight increases in lateral ventricular volume were associated with decreases in visual acuity for the left eye. Kramer et al. (2020) found evidence for altered CSF hydrodynamics, as well as increased total brain volume and increased CSF volume associated with long-duration spaceflight (Kramer et al. 2020). However, while weightlessness-induced fluid redistribution during spaceflight may be a common stressor to the brain and retina, the development of optic disc edema may be uncoupled with changes occurring in the intracranial compartment (Marshall-Goebel et al. 2021a). Changes in the eye and brain associated with SANS and long-duration spaceflight persist for at least one year after landing (Hupfeld et al. 2020; Kramer et al. 2020; Macias et al. 2021; Macias et al. 2020), and the long-term effects are only recently being studied.

Changes in cerebral blood flow as a result of microgravity exposure may also contribute to the brain functional changes described above. Following spaceflight, astronauts have reduced arterial pressure and cerebral blood flow velocity as measured with transcranial Doppler (Bondar et al. 1994). Similarly, astronauts show reduced cerebral blood flow pulsatility, as measured with impedance rheography, when in a head-down tilt posture following spaceflight (Charles et al. 1996; Gazenko et al. 1981; Watenpaugh and Smith 1998). Other studies have demonstrated a microgravity dose-dependent effect, with cerebral vasoconstriction following long-term flight remaining unresolved after a period of five weeks (Gazenko et al. 1981). It is thought that this increased vasoconstriction is an adaptive response to the increased cranial pressures experienced while in the microgravity environment.

Reorganization of Visual and Vestibular Systems

One recent study of 11 cosmonauts tested task-based functional connectivity during plantar stimulation after long-duration spaceflight. This group found connectivity changes within sensorimotor, visual, proprioceptive, and vestibular networks (Pechenkova et al. 2019). Without measures of pre- to post-flight behavioral changes, the functional significance of these results is not fully clear. The authors suggest that such changes represent reorganization of the sensory and vestibular systems and provide some evidence for multisensory reweighting with flight.

Cebolla et al. (Cebolla et al. 2016) recorded EEG as astronauts performed a visual attention task before, during, and after spaceflight. Astronauts performing the visual task while free-floating on the ISS showed reductions in alpha and mu power over occipital, parietal, and central brain regions, respectively. This finding suggests reduced inhibition of other sensory signals when visual input is available in microgravity. Such sensory reweighting may reflect increased reliance on somatosensory inputs for adjusting or stabilizing body posture while free-floating (Cebolla et al. 2016; Hupfeld et al. 2021b; Noohi et al. 2019).

Hupfeld et al. (Hupfeld et al. 2021a) measured brain activity in response to vestibular stimulation via a pneumatic tactile pulse system before and after long duration spaceflight. While the somatosensory and visual cortices are typically deactivated during this vestibular stimulation, widespread reductions in deactivation of these regions were found from pre- to post-flight, providing evidence for sensory reweighting. In addition, these pre- to post-flight changes in brain activity were correlated with declines in eyes-closed standing balance. These findings suggest that spaceflight-induced sensory reweighting and adaptive neuroplasticity of vestibular processing help explain post-flight decrements in vestibularly mediated behaviors (e.g. posture and locomotion).

Gray Matter Volume

A population of 27 astronauts who completed either approximately two-week shuttle missions (n = 13) or six-month ISS missions (n = 14), showed increased gray matter volume within medial primary sensorimotor cortex—the area of the brain that represents the lower limbs (Koppelmans et al. 2016). Structural plasticity within lower limb somatosensation and motor control brain areas may reflect a mechanism to increase the gain of somatosensory inputs in microgravity (Noohi et al. 2019). Interestingly, this finding of structural plasticity in the sensorimotor cortex could relate to the increased alpha and mu oscillations recorded in astronauts (Chéron et al. 2006), as each of the effects identified in this study were reported only in central and parieto-occipital regions, but not in the frontal cortex.

The evidence of structural changes appears to differ based on flight duration. In particular, one study found pre- to post-flight increases in periventricular white matter hyperintensities and ventricular volumes in astronauts who completed long-duration missions but not in astronauts who completed shuttle missions (Alperin et al. 2017). Twelve months in space were found to result in larger changes across multiple brain areas involved in sensorimotor processing when compared to changes found in six-month missions (Hupfeld et al. 2020). This duration effect was more apparent for brain fluid shifts than for other structural brain changes, suggesting that brain free water and ventricular volumes may be especially affected by long-duration spaceflight.

In another recent study, astronauts returning from longer duration missions showed smaller decreases in cerebellar white matter structure in comparison to astronauts returning from shorter flights (Lee et al. 2019b). While seemingly paradoxical, these findings may reflect an adaptive process whereby white matter structural organization is initially disrupted then becomes more robust over time during spaceflight.

Postflight Recovery

A small number of neuroimaging studies have assessed post-flight brain changes. However, these measures typically occur days to weeks after the landing date. One such MRI study considered functional brain activity that was collected on average 9.4 days post-flight to represent flight-related changes (Pechenkova et al. 2019). As noted by the authors, this long delay between landing and the MRI scan makes it difficult to interpret whether the results they report were due to the direct effects of flight, neural readaptation to Earth's gravity, or to a combination of these effects.

Few studies have acquired multiple post-flight measurements to track recovery trajectories of flight-related changes. For instance, one study found ventricular volume increases from pre- to post-flight; in a subset (n = 7) of the cosmonauts tested, these increases had partially recovered but were still evident at seven months post-flight (Van Ombergen et al. 2019). Another recent study (Kramer et al. 2020) reported persistent elevation of total brain volume and CSF one year after long-duration spaceflight, suggesting long-lasting alterations to brain structure following multi-month missions on the ISS. Similarly, recovery of most brain structural changes back to baseline levels were reported by 6-months post-flight for missions lasting from six to twelve months (Hupfeld et al. 2020).

B. Ground-based Evidence (ground analogs and general terrestrial research)

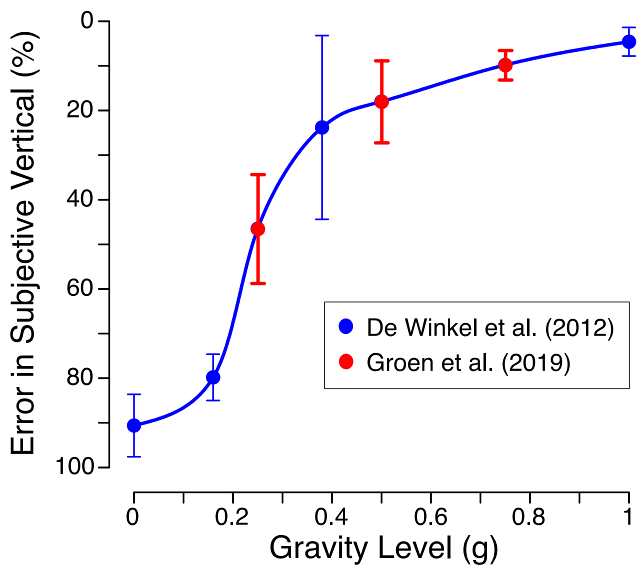
In physiology, a graded dose-response curve relates the stimulus input to a specific measured output. Space studies in humans and animals have provided only a snapshot into understanding the role of gravity on physiological responses. Fully understanding this relationship, including adaptive mechanisms, will provide the information required to ensure normal physiological function in crew for long-duration space missions. Various methods can be used for generating altered gravity, including orbital flight, parabolic flight, head down/up tilt, body loading/unloading, and centrifugation (Clement et al. 2019; Clément et al. 2019a; Goswami et al. 2021a).

1. Parabolic Flight

Spatial Orientation

Few studies have investigated the perception of verticality in partial gravity, i.e., between 0 g and 1 g, and, when doing so, showed inconsistent results. Harris et al. (Harris et al. 2012) found no effect of lunar gravity (0.16 g) on the oriented character recognition test

(OCHART) compared to normal gravity. In contrast, De Winkel et al. (de Winkel et al. 2012) found that the SVV was predominantly aligned with the longitudinal body axis under lunar gravity, whereas under Martian gravity (0.38 g) the SVV was predominantly aligned with the gravito-inertial acceleration vector (Figure 11).



Error in the subjective vertical (i.e., difference between the perceived tilt angle and the actual tilt angle relative to the gravitational vertical) in the dark in six subjects during a 90º static roll body tilt in parabolic flight at 0 g, 0.16 g, 0.38 g, and 1g (de Winkel et al. 2012), and in 6 subjects during static roll body tilt ranging from 5º to 60º at 0.25 g, 0.5 g, and 0.75 g. (Meskers et al. 2021). Mean ± SD.

Figure 11. Subjective vertical during partial-g parabolic flight

In both studies, the angle of body tilt itself was not manipulated: the participants were either seated upright (Harris et al. 2012) or lying on their side (de Winkel et al. 2012). A recent study was performed in partial gravity during parabolic flight by investigating the subjective visual vertical (SVV) at various angles of roll body tilt at three gravity levels (0.25 g, 0.75 g, 1 g) (Meskers et al. 2021). It is well known that for large angles of body tilt, SVV in the dark show a bias towards the longitudinal body axis, reflecting a systematic underestimation of self-tilt (Howard 1982). The results in the parabolic flight study showed that perceived self-tilt was even more underestimated in partial gravity conditions than in 1 g. In fact, the lower the gravity level, the larger this underestimation (Figure 11). The results of this study might explain why the Apollo astronauts tended to underestimate their self-tilt when on the Moon surface (Goodwin 2002).

Distance Perception

The perception of the horizontal and vertical distances of a visual target to an observer was investigated in parabolic flight during alternating short periods of normal gravity (1 g), microgravity (0 g), and hypergravity (1.8 g). Subjects underestimated horizontal distances as distances increased, and this underestimation decreased in 0 g, as observed during spaceflight using natural visual scenes. Vertical distances for up targets were overestimated and vertical distances for down targets were underestimated in both 1 g and 1.8 g. However, this vertical asymmetry was absent in 0 g (Clément et al. 2020a).

Time Perception

The accuracy for estimating durations of 3.5 s, 7 s, and 14 s was investigated during short periods of 0 g, 1 g, and 1.8 g during parabolic flight. Duration estimates were measured using reproduction and production of duration in two conditions: a control counting condition and a concurrent reading condition. Simple reaction times were also measured to assess attention. The results showed that the temporal accuracies during the reproduction task in the concurrent reading condition were significantly underestimated in 0 g compared with 1 g. Reaction times were also longer in 0 g. However, there was no difference in duration estimates in the production tasks (Clément 2018). The author suggests that the temporal underestimation in 0 g is caused by decreased selective attention and impaired retrieval of information in episodic memory.

Mass Perception

When tested during parabolic flight, participants overestimated the weight of their hand and head in hypergravity (1.8 g) and underestimated these weight in microgravity (0 g) compared to normal terrestrial gravity (1 g) (Ferre et al. 2019).

In another study, subjects were asked to assess perceived heaviness by actively oscillating objects with various sizes and masses (Clément and Wood 2014). After lifting two objects with identical mass but different sizes, participants reported that the small object felt heavier than the large object. This *perceptual* size-mass illusion was present in 1 g, 0 g, and 1.8 g. However, during the oscillations, the peak arm acceleration varied as a function of the gravity level, irrespective of the mass and size of the objects, indicating an absence of *sensorimotor* size-mass illusion. These findings indicate dissociation between the sensorimotor and perceptual systems for determining object mass, which could pose a problem for astronauts on the Moon or Mars when determining the relative difference in mass between objects.

Ocular Alignment

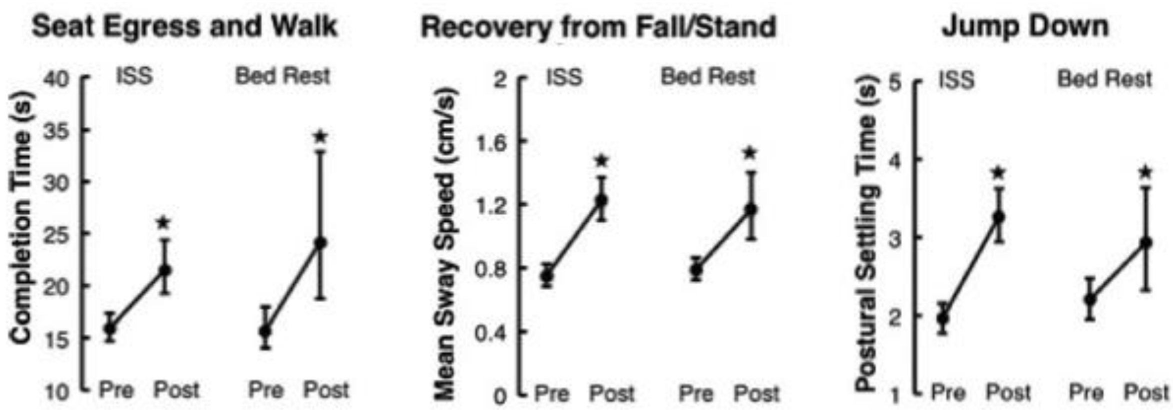
Vertical and torsional ocular positioning misalignments elicited by 0 g and 1.8 g in parabolic flight have been studied using Vertical Alignment Nulling (VAN) and Torsional Alignment Nulling (TAN). Subjects exhibit significant differences in ocular misalignments in 0 g and 1.8 g, which could be the result of tuned central compensatory mechanisms not adapted to the parabolic flight environment. Increased ocular positioning misalignments upon exposure to altered gravity levels have been strongly correlated with space motion sickness severity, possibly due to underlying otolith asymmetries uncompensated in novel gravitational environments (Beaton et al. 2015).

2. Head-Down Bed Rest

Extended periods of -6 deg head-down bed rest (HDBR) is a model frequently used for spaceflight that simulates the effects of spaceflight on the cardiovascular, ocular, and sensorimotor systems (Cromwell et al. 2018). It also provides an experimental paradigm to examine combinations of stressors, e.g. fluid shifts and elevated CO_2 (Clément et al. 2022), and a ground-based evaluation of complex countermeasures (Frett et al. 2020).

Behavioral Studies

Subjects' performance on functional tests that challenge the balance control system (Seated Egress and Walk; Object Translation; Recovery from Fall/Stand; and Jump Down) and clinical tests of balance function (Computerized Dynamic Posturography and Tandem Walk) were examined after long-term axial body unloading during 70 days of HDBR. Data were collected twice during the 2-week period before bed rest, and four times after bed rest. Long-term axial unloading alone caused functional performance deficits immediately after bed rest, similar to those observed in astronauts immediately after landing (Miller et al. 2018) (Figure 12). Other changes after HDBR included reduced lower limb muscle performance and increased HR to maintain blood pressure. Exercise performed during bed rest prevented detrimental change in neuromuscular and cardiovascular function; however, both bed rest groups experienced functional and balance deficits similar to spaceflight subjects (Mulavara et al. 2018).



*Changes in performance metrics before (Pre) and after (Post) 6-month stays on the ISS and 70-day bed rest. * P < 0.05 (Miller et al. 2018).*

Figure 12 Changes in FTT following ISS and HDBR

Reports have indicated that crewmembers onboard the ISS experience symptoms of elevated CO_2 such as headaches at lower levels of CO_2 than levels at which symptoms begin to appear on Earth. This suggests there may be combinatorial effects of elevated CO_2 and the other physiological effects of microgravity including headward fluid shifts and body unloading. The VaPER (VIIP and Psychological :envihab Research) study was performed to investigate these effects by evaluating the impact of 30 days HDBR and 0.5% CO_2 on mission relevant cognitive and sensorimotor performance. A decrement in functional mobility was found in subjects of the VaPER study compared to previous studies in ambient air (Lee et al. 2019a). By contrast, spatial working memory improved during the HDBR + CO_2 study (Salazar et al. 2020). In addition, nearly half of the VaPER participants developed signs of Spaceflight Associated Neuro-ocular Syndrome (SANS). Participants who exhibited signs of SANS became more visually dependent and were slower but more accurate than those that did not incur ocular changes (Mahadevan et al. 2021). In addition, the SANS and No SANS subgroups exhibited distinct patterns of resting-state functional connectivity changes during HDBR+CO_2 within visual and vestibular-related brain networks (McGregor et al. 2021b). These small subgroup findings suggest that SANS may have an impact on mission relevant performance inflight via sensory reweighting (Lee et al. 2019a).

Brain Imaging Studies

During -6 deg head-down bed rest (HDBR), increased brain activity was observed during vestibular stimulation (Yuan et al. 2018b) and during performance of a cognitive-motor dual task (Yuan et al. 2016), compared to matched controls who did not participate in HDBR. These findings suggest that extended periods of microgravity simulation might evoke the need for greater neural resources (i.e., reduced neural efficiency) while processing cognitive and sensori-motor information. Brain imaging studies are also providing insight into changes in the neural control of foot movement that may help some of the postural and locomotion decrements (Yuan et al. 2018a).

Long-duration HDBR results in similar fluid shifts towards the head and unloading of the body as in microgravity (Lee et al. 2021). As such, apparent increased brain gray matter volume in posterior parietal cortex and decreased gray matter volume in frontal areas were also observed during HDBR (Koppelmans et al. 2017). Roberts et al. (Roberts et al. 2015) also observed crowding of the cerebrospinal fluid (CSF) around the vertex and an upward shift of the brain within the skull.

Novel postprocessing has also been applied. With body unloading in HDBR, subjects experience reductions in lower limb use. Transcranial magnetic stimulation was used to assess changes in motor cortex excitability in humans who wore a full leg cast (on Earth) for 10 days. Measures of this excitability significantly increased following leg cast removal (Roberts et al. 2007). An association was also observed between *greater* brain activation during foot tapping at the end of 70 days of HDBR and *better* post-HDBR balance and mobility (Yuan et al. 2018b). This suggests a compensatory response in which, in order to sustain smaller reductions in balance and mobility, individuals require greater neural resources for lower limb motor control to compensate for the down-weighting of foot neural representations during HDBR.

In another study, in which subjects underwent 30 days of HDBR combined with elevated CO_2, further support for adaptive neural changes was observed within the vestibular (Hupfeld et al. 2019) and spatial working memory (Salazar et al. 2021; Salazar et al. 2020) systems. For instance, multiple regions in which *greater* pre- to post-HDBR deactivation of certain vestibular brain regions were associated with *less* balance declines following HDBR (i.e., greater preservation of balance performance). However, the addition of elevated CO_2 during HDBR had minimal effects brain activity during visuomotor adaptation (Salazar et al. 2021) and dual tasking (Mahadevan et al. 2021) compared to HDBR alone.

Similar to after spaceflight, gray matter volume increases within medial primary sensorimotor cortex following 70 days of HDBR (Koppelmans et al. 2017). Greater gray matter volumetric increases within this region following HDBR were associated with *smaller* decrements (and in some cases improvements) in standing balance performance (Koppelmans et al. 2017). After HDBR, recovery of brain changes occurs as rapidly as about two weeks days post-HDBR (Cassady et al. 2016; Koppelmans et al. 2017; Lee et al. 2019a; Lee et al. 2021; Yuan et al. 2018b; Yuan et al. 2016). For instance, increased gray matter volume in somatosensory cortex was seen at seven days post-HDBR compared to pre-HDBR, but by 12 days post-HDBR, this difference was no longer significant (Koppelmans et al. 2017).

3. Horizontal or Tilted Axis Paradigms

Rotating a subject about an Earth vertical axis to minimize gravitational cues provided an analog environment for Preflight Adaptation Training (PAT-DOME, Harm and Parker 1994). A similar strategy has been used recently to explore closed-loop nulling of tilt disturbances when tilted about Earth-horizontal and vertical axes (Vimal et al. 2021; Vimal et al. 2016). Diaz-Artiles and colleagues have used tilt tables to examine the influence of gravity on bimanual coordination (Diaz-Artiles et al. 2021). Another approach is to utilize the combination of translational and tilt motion to simulate tilt-translation illusions, e.g., the Tilt-Translation Device (PAT-TTD, Harm and Parker 1994). Wood and colleagues developed a Tilt-Translation Sled to create a 'GIF aligned' paradigm that was patterned after experiments to examine neural strategies of resolving tilt-translation ambiguity (Angelaki et al. 1999) and examine motion sickness on tilting trains (Golding et al. 2003). This 'GIF aligned' paradigm mimics the mismatch between canals and vision that signal tilt and otolith input and is therefore like the pattern of sensory cues experienced on orbit. This paradigm was used for both ground-based studies of tilt-translation adaptation (Kayanickupuram et al. 2010) as well as a test platform for pre- versus post-flight studies (Clément et al. 2008).

Recently Clark and colleagues developed another analog involving subjects lying on their side on a bed fixed to a modified electric wheelchair with their head restrained by a custom facemask. This wheelchair head-immobilization paradigm (WHIP) prevents any head tilt relative to gravity, which normally produces coupled stimulation to the otoliths and semicircular canals but does not occur in microgravity. Decoupled stimulation is produced through translation and rotation on the wheelchair by the subject using a joystick. Following 12 hours of WHIP exposure, subjects systematically felt illusory sensations of self-motion when making head tilts and had significant decrements in balance and locomotion function using tasks like those assessed in astronauts after spaceflight. These effects were not observed in the control groups without head restraint, suggesting the altered neurovestibular stimulation patterns experienced in WHIP lead to relevant central reinterpretations (Dixon and Clark 2020).

4. Centrifugation & Slow Rotating Rooms

Landmark rotating room studies were performed in the 1960s at the Naval Aerospace Medical Research Laboratory in Pensacola, FL. These studies were conceived to examine the feasibility of an artificial gravity type countermeasure (Graybiel et al. 1965); however, the pre- and post-rotation adaptation provided a time course of adaptation analogous to spaceflight (Guedry et al. 1998). While the early rotating room studies were limited to low angular velocities (3 - 4 rpm), more recent research has focused on adaptation to higher velocities (e.g., 10 rpm, Lackner and DiZio 2003) that would be needed for intermittent approaches implemented on shorter radius centrifuges.

Exposure to sustained centrifugation provides another analog environment to study G-state adaptation in head movement induced postural imbalance, illusory surround motion, and nausea (Albery and Martin 1996; Groen et al. 2011). This centrifugation is well tolerated in the subject's front-to-back (Gx) axis for periods up to 90 min. The similarities to space motion sickness (SMS) were first observed by three European scientist astronauts (Bles et al. 1989; Ockels et al. 1990), then subsequently performed on additional astronauts. Post-centrifugation motion sickness ratings of 14 astronauts and cosmonauts showed a strong positive correlation with their SMS symptoms severity (Bos et al. 2012; Groen et al. 2011). There is a hypersensitivity to head movements, especially those involving a reorientation relative to gravity (Bles et al. 1997; de Graaf and de Roo 1996). While 30 min at 3G is sufficient to induce changes in dynamic cerebral autoregulation (Serrador et al. 2001), 90 min has resulted in greater post-centrifugation motion sickness symptom severity than 40-45 min at both 2Gx and 3Gx resultant gravitoinertial force levels (Albery and Martin 1996; Nooij and Bos 2007).

A long-radius centrifuge has been recently used to study manual control performance in hypergravity (Clark et al. 2015a). In the dark, subjects were tasked with nulling out a pseudo-random roll disturbance on the cab of the centrifuge using a rotational hand controller to command their roll rate in order to remain perceptually upright. Subjects overestimated roll tilts in hypergravity and their manual control performance degraded by 26% and 45% in 1.5 g and 2 g, respectively. Manual control performance errors were reduced both with practice and with pre-exposure to alternate hyper-gravity stimuli. Tilting supine subjects relative to a centripetal force vector on a short-radius centrifuge has also been used to create a type of hypogravity analog. Using this paradigm, relative to hypergravity subjects tended to underestimate roll-tilt magnitude (Galvan-Garza et al. 2018) and manual control was degraded (Rosenberg et al. 2018).

5. Isolation and Confinement

NASA’s Extreme Environment Mission Operations (NEEMO) is a space-flight analog mission conducted within Florida International University’s Aquarius Undersea Research Laboratory (AURL). NEEMO is the only existing operational and habitable undersea environment designed for studying 9-10 days hyperbaric and/or saturated (HBS) environment. Recent studies found that aquanauts exposed to saturation over 9 –10 days experienced intrapersonal physical and mental burden, sustained good mood and work satisfaction, decreased heart and respiratory rates, increased parasympathetic and reduced sympathetic modulation, lower cerebral blood flow velocity, intact cerebral autoregulation and maintenance of baroreflex functionality, as well as losses in systemic bodyweight and adipose tissue (Koutnik et al. 2021). NEEMO has also been used to develop equipment to independently and quickly assess changes in performance of static posture, tandem gait, and lower limb ataxia due to exposure in an extreme environment. Data reveal changes in upper body balance and gait irregularity during tandem walking over the duration of mission exposure (Kim et al. 2018).

C. Evidence from other organisms (animal, cells)

Animals were used in the early years of the space age to help determine if humans would be able to survive short-duration spaceflight. Although the advent of spaceflight provided an opportunity to study fundamental biological principle(s) of how an animal’s CNS responds to weightlessness, we still do not know how the CNS adapts to rapid transitions in gravity levels or whether animals and humans respond in a similar manner. Nevertheless, behavioral and physiological results in model organisms might offer clues in understanding the underlying mechanisms affecting human neural processing in spaceflight. Below we review the pertinent results of these animal studies related to crew health and performance on exploratory missions and the potential causes of the observed changes (see review in Clément et al. 2020b). Given the implications for countermeasures, additional data will need to be obtained to fully leverage our understanding of adaptive neural processes (Boyle 2021).

The radiation environment in exploration class missions poses a greater threat to the CNS than the environment for ISS astronauts since they are partially protected by the Earth. During a short-duration mission, astronauts may experience detrimental CNS changes in cognition, short-term memory, motor function, and behavior. Late responses to radiation damages can include premature aging, Alzheimer's disease, or other dementia (Cucinotta et al. 2014). A recent report indicates there were no differences in cardiovascular disease mortality rate between astronauts who flew in low Earth orbit (11%) and astronauts who never flew in space (9%) However, the mortality rate among Apollo lunar astronauts (43%) was 4-5 times higher than in LEO and non-flight and astronauts (Delp et al. 2016). The authors proposed that the combination of microgravity and radiation could induce a sustained vascular endothelial cell dysfunction leading to occlusive artery disease in astronauts exposed to deep space radiation.

Radiation exposure in low Earth orbit is ultimately caused by galactic cosmic rays (GCR) and solar particle events (SPEs). Although all dose regimens have the potential to cause decrements in performance and cognition, it is the low to moderate levels (~ 1 to 2 Gy) of charged-particle exposure that will define the space radiation environment for crewmembers during long-duration spaceflights (Nelson 2009). A study in which mice were exposed to 0.1 and 1 Gy of whole-body proton irradiation showed dendritic complexity was significantly dependent upon dose reduction, and the number and density of dendritic spines along hippocampal neurons of the dentate gyrus was significantly reduced (Parihar et al. 2015).

The brain may also undergo structural remodeling as a result of microgravity exposure, radiation exposure, and vascular changes associated with spaceflight (Carpenter et al. 2010). The brain's structural organization is not fixed but rather can undergo extensive remodeling, even in the adult brain. These changes occur in response to skill learning (Kami et al. 1995), recovery from brain insult such as stroke (Cramer et al. 1997), and as a result of cognitive training (Olesen et al. 2004). Moreover, brain plasticity occurs as a result of disuse such as prolonged bed rest (Roberts et al. 2010).

Animal studies have shown that microgravity exposure results in structural brain changes. Research with rats has demonstrated that brain structural changes occur as a result of microgravity exposure, particularly in the somatosensory cortex (D'Amelio et al. 1998; Krasnov 1994; Newberg 1994) and cerebellum (Holstein et al. 1999; Holstein and Martinelli 2003). These changes include decreased synapses and degeneration of axonal terminals. It has been has demonstrated that hair cells in the rat utricular macula undergo extensive plasticity as a result of spaceflight, with a large (40-55%) increase in synapse number (Ross 1993; Ross 1994; Ross 2000; Ross and Varelas 2003). This plasticity remained evident following the flights, even after posture control in the rats had returned to normal. Therefore, in humans, potential structural changes associated with long-duration spaceflight could have behavioral implications for both spaceflight operations and long-term health of crewmembers. Studies are currently being conducted with ISS crewmembers that will identify potential changes in brain structure and function following long-duration spaceflight using magnetic resonance imaging techniques to assess the risks of changes in brain structure and the impact on sensorimotor and cognitive function.

1. Vestibular Neural Activity

In microgravity, the toadfish increased their afferent sensitivity to restore their ability to detect acceleration. In addition, these fish behaved erratically when provoked during the first day after landing. Although some afferents remained hypersensitive for days after spaceflight, on average, afferent sensitivity (and behavior) returned to normal within 24-36 h of landing, similar to the recovery time for vestibular disorientation in astronauts after they return from space (Boyle 2019; Boyle 2021; Boyle et al. 2018). The mechanisms involved in these peripheral vestibular changes during transitions between gravity levels could include (a) changes in sensitivity of the hair cell transducer; (b) temporary structural alterations affecting the mechanoreception of the otolith; or (c) pre- or postsynaptic alterations in the strength of synaptic transmission.

Ross (Ross 2000) provided evidence that weightlessness-induced hypersensitivity of the otolith afferent could be due to presynaptic adjustment of synaptic strength in the hair cell. In rats, the number of synaptic ribbons in certain type II hair cells increased by ~55% after exposure to weightlessness, whereas the type I hair cells were less affected. Because toadfish possess only type II hair cells, an increase in synaptic strength could be an initial adaptive response to restore the absence of gravity detection which is then followed by a deletion of the added synaptic bodies (Graydon et al. 2017), leading to restoration of normal function after return to a gravity environment.

Cohen et al. (Cohen et al. 2005a) recorded the activity of central vestibular neurons and monitored ocular gaze in alert monkeys during spaceflight. They found that vestibular neurons increased in sensitivity early in the missions. In contrast, a recent study showed that astronauts' otolith-mediated responses elicited by centrifugation were decreased immediately after return from 6 months of spaceflight and fully recovered within 9 days of return (Hallgren et al. 2016).

Animal studies showed that hippocampal "place" cells retain their three-dimensional spatial selectivity during spaceflight, suggesting a remarkable resolution of self-motion and external landmark cues in such a novel environment (Knierim et al. 2000; Knierim and Rao 2003). Animal studies have also shown that microgravity exposure results in structural brain changes. For example, research with rats has demonstrated that microgravity exposure results in structural changes particularly in the somatosensory cortex (D'Amelio et al. 1998; Holstein et al. 1999; Krasnov 1994; Newberg 1994) and cerebellum (Holstein et al. 1999). These effects include decreased synapses and degeneration of axonal terminals. Electron microscopic examination of the cellular organization of the adult rat cerebellar nodulus, a zone that receives significant input from vestibular otolith afferents, revealed structural and molecular changes (Holstein and Martinelli 2003; Pompeiano et al. 2004).

In addition, exposure to weightlessness attenuated the function of the arterial baroreceptor reflex in young rats that were still developing, and this blood pressure control system returned to baseline level 30 days after landing (Waki et al. 2005). The absence of gravity during a 16-day space mission permanently prevented the maturation of motor tactics for surface righting in postnatal rats, whereas the loss of contextual interaction in space was transient in postnatal rats that spent 9 days in space (Walton et al. 2005).

Hypothalamic and brainstem centers, as well as the sympathetic nervous system, have been identified as regulators of bone remodeling (Vico and Hargens 2018). However, the nature of the afferent stimuli that may modulate brain centers involved in the control of bone remodeling, with the exception of leptin, remains unclear. Bone analyses in rats following bilateral vestibular lesions indicated significant bone loss in weight-bearing bones associated with a significant reduction in bone formation, as observed in rats under microgravity conditions (Vignaux et al. 2013). This bone loss was accompanied with molecular signs of increased sympathetic outflow, suggesting that the homeostatic process of bone remodeling has a vestibulosympathetic regulatory component.

Although partial gravity can only be generated for brief moments on Earth, hypergravity can be delivered for extended periods in ground-based studies and can be used to determine whether structures and their functions respond linearly to gravity levels. Boyle et al. (Boyle et al. 2018) used toadfish to study how utricular afferents respond to translational accelerations after a Space Shuttle mission and after 1-32 days of centrifugation at 2.24 g. Because the afferents were hypersensitive after spaceflight, the authors expected they would be hyposensitive in hypergravity. Unexpectedly, the toadfish utricular afferents exhibited hypersensitivity after 3 days of centrifugation, which intensified on the fourth day and then returned to normal levels during days 5-8, and the (anticipated) hyposensitivity occurred during days 16-32. The initial hypersensitivity and later hyposensitivity required more than 4 and 2 days, respectively, of exposure to 1 g to recover to control levels. Since the initial afferent response is elevated in toadfish during centrifugation, and the afferent response in bullfrogs and central vestibular neuron response in primates are elevated during the first days of spaceflight, this might reflect a consistent early neural reaction to a gravity challenge in either direction: weightlessness or hypergravity. Prolonged exposure to hypergravity leads to a later reduction in afferent sensitivity. While the afferent response to prolonged exposure to weightlessness is still unknown, it might also develop a hyposensitivity over time. This initial reaction is in line with the astronauts' disorientation during the first days of a space mission.

Recently, Sultemeier et al. (Sultemeier et al. 2017) showed that spaceflight decreases synaptic densities in the mouse extrastriolar utricle, which is in opposition to findings from a study in rats (Ross 2000) that showed synaptic densities increased during spaceflight. Interestingly, the horizontal semicircular canal afferent sensitivity to angular rotation was unaffected by centrifugation in fish (Boyle et al. 2018), and synaptic densities of hair cells in the horizontal semicircular canal of rats were unchanged by spaceflight (Sultemeier et al. 2017).

The physiological basis of spatial orientation perception became better understood with the discovery in rat and primate limbic systems of place cells that code the direction the animal is facing, independent of head movement. Also discovered were grid and place cells that code various attributes of location relative to visual landmarks (Wiener and Taube 2005), analogous to a map of the local environment. All three classes of cells respond in a navigation coordinate frame normally defined by the plane of locomotion, even in 0 g and hypergravity (Knierim et al. 2000; Taube et al. 2004). How larger (geo) scale environmental knowledge is coded is not yet understood, but clinical evidence from patients with poor geospatial abilities suggests that these same limbic structures at least participate.

2. Utricular Otolith Asymmetry

The possibility that weightlessness affects neural development, structure, and function are of critical concern for long-term space missions. We do know that short-term exposure to weightlessness dramatically alters vestibular function: simple animal experiments with clear hypotheses have provided particularly meaningful conclusions.

On Skylab in 1975, fish (mummichogs, *Fundulus heteroclitus*) housed in a plastic bag were strongly disoriented and swam in loop at *day 3* (first recording) of the mission. At *day 22* (second recording) of the mission, their behavior returned to normal; however, the aberrant behavior could still be evoked by a slight shake of the bag (Von Baumgarten et al. 1975). Toadfish (*Opsanus tau*) returning from flights on board the Space Shuttle were uncharacteristically agitated, swam violently, and sought "terra firma" (Boyle et al. 2001).

Cichlid fish (*Oreochromis mossambicus*) that flew on the Space Shuttle, sounding rockets, or parabolic flights also exhibited this "looping" behavior (Anken et al. 2000; Hilbig et al. 2002). Researchers observed that the abnormal looping and spinning were positively correlated with differences in the mass of the right and left utricular otoliths, suggesting that weightlessness unleashed the adapted response of fish to a normally occurring asymmetry between their otoliths. In addition, the fishes (salmon, trout, green swordtail, or Sumatra barb) that exhibited abnormal swimming behavior during off-vertical axis rotation on Earth had statistically greater asymmetry in their otoliths than fish that swam normally in the same experimental conditions (Scherer et al. 2001).

The magnitude of the otolith asymmetry in an individual animal is likely a key factor in triggering abnormal behaviors in weightlessness (Lychakov et al. 2006). Along these lines, other fishes, such as goldfish and carp, display both negligible structural asymmetry and marginal abnormal behavior in weightlessness (Takabayashi and Ohmura-Iwasaki 2003). As attractive as this otolith asymmetry hypothesis is in explaining the susceptibility of humans to motion sickness induced by spaceflight or other stimuli (Lychakov and Rebane 2005; von Baumgarten et al. 1987; Yegorov and Samarin 1970), it is difficult to correlate an overt abnormal behavior in fish to a subjective sensation in humans, and the human otoconia mass is more complex than that of the fishes' single otolith. More data is needed from other vertebrate species, most notably mammals including primates, to prove this theory.

3. Plasticity of Invertebrate Statocyst

Spaceflight also induces plasticity in the vestibular system of invertebrates. Receptor cells in the statocyst of the land snail (*Helix lucorum*) were studied using a variety of approaches after the snails returned from the unmanned Foton orbital missions M2 or M3 (Balaban et al. 2011) or the Bion-M1 (Aseyev et al. 2017) Russian biosatellite mission. The stereotypic behavior evoked by the "negative gravitaxis" test, a reliable measure of vestibular function, was directly compared with the discharge properties of individual statoreceptors in the same animal after landing. About 13 h after landing, statoreceptor responses to head-down pitch were faster and more sensitive in the snails who had flown in space than in the control animals. The snails' tilt responses recovered to baseline ~20 h after return to Earth, similar to the time required for recovery of afferent responses in toadfish after they returned from space. Although the snails' statocyst activities were recorded directly from the statoreceptors themselves, and the hypersensitivity observed in the toadfish was recorded in the afferent that is postsynaptic to the receptor, the changes in sensitivity in invertebrate statoreceptors match those seen in vertebrate afferents. Invertebrates have genes for one or more subfamilies of transmembrane channel-like proteins (Keresztes et al. 2003), which are thought to have a role in mechanosensory transduction channels in inner ear hair cells. If these proteins are involved in a pore-forming component of sensory transduction channels in the statoreceptors, then a common mechanism might exist across the animal phyla. However, no direct evidence exists on how otolith hair cells function in vertebrates during spaceflight.

4. Otolith Mass

Vertebrates sense gravitoinertial acceleration by mechanoreceptors in the otolith organs of the inner ear. These structures consist of ciliated sensory hair cells with otoconia (small crystals of calcium carbonate) placed on top that stimulate the cells when moved due to linear acceleration or tilt in gravity. Inner ear structures are believed to regulate their function through adaptive processes by increasing or decreasing production of calcium carbonate in response to a sustained decrease or increase in the amplitude of gravity, altering otolith mass and subsequent transduction gain of the system. A number of studies support the hypothesis that the mass of the otoconia increases in weightlessness. For example, the masses of the sacculus and the utricle in animals that matured in space, such as freshwater pond snail (Wiederhold et al. 2000), marine mollusk (Wiederhold et al. 1997), frog (Anken et al. 2000; Lychakov and Lavrova 1985), newt (Wiederhold et al. 1996), and swordtail fish (Wiederhold et al. 2000), were greater than that in ground-matured controls. As expected, the Otoconia masses were smaller in sea slugs *Aplysia californica* (Pedrozo et al. 1996) and cichlid fish (Wiederhold et al. 2000) that were born in hypergravity than in controls. Using cichlids, researchers (Anken et al. 2000; Li et al. 2011) have shown that a neutrally guided feedback mechanism adjusts the biomineralization of otoliths in response to changing gravity levels: hypergravity induced by centrifugation slows down otolith growth, whereas weightlessness leads to larger than normal otoliths. Aceto et al. (Aceto et al. 2015) reported a decrease in otolith calcification in zebrafish after prolonged centrifugation. These changes are presumed to be the result of a regulation of carbonic anhydrase and production of other matrix proteins (Anken 2006; Anken et al. 2004).

Boyle et al. (Boyle et al. 2015) used electron microscopic techniques to image otoconia masses obtained from (a) mice exposed to both 91-days of weightlessness in the ISS and 91-days of 2 g centrifugation on ground, and (b) mice flown on short-duration Shuttle missions. Results from ISS showed a clear restructuring of individual otoconia with increased deposition and mass while the 2 g counterparts showed a decrease in otoconial mass. Conversely, for shorter duration exposures to weightlessness (13-days), the otoconia appeared to be normal. Therefore, long-duration exposure to spaceflight may induce adaptive mechanisms that lead to structural alterations in peripheral end organ transduction of motion contributing to behavioral disturbances.

More recently, Boyle and Varelas (Boyle and Varelas 2021) reported changes in otoconia structure in several strains of mice after short- and long-duration exposures to altered gravity. Although no changes were observed in mice exposed to 13 days of Shuttle Orbiter flight or 90 days of hindlimb unloading, a possible mass addition to the otoconia outer shell was observed in mice flown on the ISS for 90 days. In contrast, an ablation or thinning of the outer shell and cavitation of the inner core was clearly seen after centrifugation. Despite being purely descriptive, these findings suggest that otoconia structural remodeling occurs in mice after exposures to altered gravity, which would have implications for countermeasure development and sensorimotor analogs.

5. Behavior of Invertebrates during Spaceflight

During the Shenzhou-8 mission, nematodes' (*Caenorhabditis elegans)* speed of locomotion, frequency of reversals, and rate of body bends were normal (Qiao et al. 2013), and during the Space Shuttle STS-42, nematodes were able to mate and reproduce for two consecutive generations on a semisolid substrate, indicating that complex controlled locomotion and mating behavior were stable in weightlessness *(Nelson 1994)*.

Drosophila flies are more active in microgravity than on Earth, especially younger flies, and spaceflight accelerated aging-like phenotypes of young males, which may have been caused by alterations in the mitochondrial metabolism. The flies' daily cycles of activity and inactivity are governed by their circadian system, so increased activity in space could be associated with disruption of sleep cycles. In hypergravity, the flies' activity changed according to the gravity level: no effect at 2 g, increased activity at 6 g, and progressively less activity as gravity level rose to 20 g (Benguría et al. 1996; Herranz et al. 2008).

Crickets have an external gravity sensory structure that is stimulated by postural displacements and induces compensatory head movements. The position-sensitive interneuron (PSI), which transfers information from the cricket's gravity sense organ to the CNS, was significantly less sensitive in weightlessness, and levels of a specific neuropeptide were elevated, perhaps reflecting compensation (Horn et al. 2002). However, the crickets' behavior was not significantly impaired, suggesting they were able to compensate effectively to weightlessness. Bees and moths also exhibited impaired locomotion in weightlessness but learned to fly over time, and the orb weaver spider's ability to build webs was impaired in space (Clément and Slenzka 2006).

6. Behavior of Amphibians and Reptiles During Spaceflight

Japanese tree frogs (*Hyla japonica*) on the Mir Space Station arched their backs and extended their limbs during free floating, similar to jumping or "parachuting" on the ground, and they were unable to properly control their locomotion and orientation. When they were on surfaces, these frogs bent their necks backward and walked backward while pressing their abdomens against the surface, which is similar to their posture on the ground when they are vomiting and may reflect motion sickness. The frogs readapted to the Earth's gravity within a few hours of return from space, and structural changes were detected in some of their organs, including the spine but not the brain (Izumi-Kurotani et al. 1997; Yamashita et al. 1997).

Geckos in weightlessness exhibited behavioral reflexes similar to a fall in normal gravity, i.e., ventral extension of the limbs, skydiving posture, and postural righting reflexes (Barabanov et al. 2019). During parabolic flight, a striped rat snake (*Elaphe quadrivirgata*) assumed a defensive posture during the shift from hyper- to hypogravity and struck at itself. Three striped-neck pond turtles (*Mauremys japonica)* actively extended their limbs and hyperextended their necks in weightlessness, which is identical to their contact “righting reflex” when placed upside down in normal gravity (Wassersug and Izumi-Kurotani 1993).

D. Computer-based Models and Simulation

While there are few robust ground-based models available for experimental investigations of the impacts of spaceflight on a crewmember’s mobility and ability to maintain control of vehicles and complex systems, many computer-based models of the vestibular system and sensorimotor control have been developed. Since these may be useful in simulating and/or predicting the impacts of physiological adaptations on operational performance, particularly under off-nominal conditions, a brief review of the relevant aspects of the field is provided in this section. Before they can be used in design and verification, though, these (and other) models must be quantitatively validated and certified using targeted empirical studies.

1. Models of Vestibular Function and Spatial Orientation

Vestibular neuroscientists have developed quantitative mathematical models for semicircular canal and otolith function, eye movements, and central nervous system (CNS) estimation of angular and linear motion perception. For example, Fernandez & Goldberg (Fernandez and Goldberg 1976) modeled the firing frequency of individual semicircular canal afferents using a linear transfer function model (Groen 1957; Oman et al. 1987) and a time constant describing neural adaptation (Young and Oman 1969). Utricular shear (Schone 1964), tangent (Correia et al. 1968), and idiotropic vector (Mittelstaedt 1983) models have also been proposed to predict static perception of tilt in altered gravity environments.

Several mathematical models have been proposed for *dynamic* orientation perception, as reviewed by MacNeilage et al. (MacNeilage et al. 2008). Concepts from engineering estimation and control theory have been employed such as Kalman filters (Borah et al. 1988), extended and unscented Kalman filters (Selva 2009), and particle filters (Karmali and Merfeld 2012; Laurens and Droulez 2007).

Young et al. (Young 1967) originally suggested that the CNS functions like an adaptive (Kalman) filter when combining sensory cues and introduced additional dynamics into vestibular responses due to these central processes. Adapting inertial guidance theory, Young (Young 1969; Young et al. 1973; Young et al. 1984) noted that laws of physics dictate that the body’s graviceptors respond to the net gravito-inertial specific force ($\mathbf{f} = \mathbf{g} - \mathbf{a}$), the physical quantity tracked by a pendulum or measured by a linear accelerometer (where $\mathbf{a}$ = linear acceleration vector and $\mathbf{g}$ = gravitational acceleration vector). A variety of different orientations and accelerations can cause the same graviceptor stimulus. The CNS must therefore use other cues to distinguish the components caused by gravity from those caused by linear acceleration. The CNS may estimate linear acceleration by maintaining an internal estimate of the direction and magnitude of ($\hat{\mathbf{g}}$) and subtracting off the graviceptor cue vector ($\hat{\mathbf{a}} = \hat{\mathbf{g}} - \mathbf{f}$). The direction of down, $\hat{\mathbf{g}}$**,** is estimated at low frequencies based on the average direction of graviceptor cues, $\mathbf{f}$, and also visual cues, if available. Visual inputs are angular and linear velocity of the visual surround with respect to the observer. At high frequencies, semicircular canal cues and body movement commands are used. If the direction of $\hat{\mathbf{g}}$ is misestimated, dramatic misperceptions of orientation and linear acceleration can result.

Although "optimality" of the human observer (in the Kalman sense) has since been discounted, the notion remains widely accepted that the CNS functions as an "observer," in the control engineering sense (Borah et al. 1988), estimating head orientation based on internal representations of the direction of gravity and sensory organ dynamics. Others have elaborated CNS observer-based models for semicircular canal-otolith interaction. For example, Raphan et al. (Raphan et al. 1979), Robinson (Robinson 1981), Merfeld et al. (Merfeld et al. 1993), and Nooij et al. (Nooij et al. 2016) developed influential observer class models for CNS estimation of head angular velocity and tilt, now often referred to as "central velocity storage" theories. Merfeld's models for canal-otolith cue interaction in "down" estimation (Merfeld and Zupan 2002) successfully predict canal-otolith cue interaction in a variety of experimental situations. They are now widely utilized in research and the diagnosis of clinical vestibular disorders. These models have occasionally been applied to aircraft accident investigation, albeit in a limited way, since they do not (yet) incorporate effects of visual cues, and data on aircraft accidents is frequently lacking.

Clark et al. (Clark et al. 2015b) recently proposed a modification to the observer model, allowing for the prediction of the static and dynamic overestimation of roll tilt experimentally observed across a range of conditions. The modification is based upon the hypothesis that the CNS treats otolith stimulation in the utricular plane different than stimulation out of the utricular plane.

2. Models of Manual Control Performance

Manual Control theory was originally developed in the 1960s, when feedback control engineers sought to analyze and predict the performance of humans in control loops and describe both the human (the operator) and the controlled system (the plant) within the same mathematical framework. The premise was that human operator performance could be approximated well using a "describing function." Both compensatory tasks (where the operator sees only an error signal) and pursuit tasks (where both the goal and plant outputs are available) have been modeled this way.

A simple and widely used principle is the "crossover model" (McRuer 1972), which posits that the operator will instinctively adopt an appropriate control strategy such that at the open loop transfer function of the operator and plant taken together resembles that of a simple integral process and a time delay in the region of the crossover frequency. The operator can perceive the rate of change of plant output and create anticipatory phase lead that counteracts phase lags due to the plant. If the plant is a vehicle, vestibular motion cues allow the operator to improve performance by creating an additional phase lead. However, the operator's transfer function is constrained. Some effective time delay is always present due to perceptual, cognitive, and muscle activation effects. Also, operators cannot respond to the second or higher derivatives of plant output. The crossover model structure and parameter values thus quantify the operator's control strategy. The model also has important emergent properties: it predicts manual control gain and bandwidth limits. It also explains why humans cannot successfully stabilize higher than second order integral plant dynamics, unless the operator is able to monitor intermediate system outputs, in effect transforming the task into concurrent (multi-loop) lower order tasks. This is why an operator cannot successfully stabilize a hovering lunar lander or a helicopter (approximately triple integral plants) over a landing spot without reference to a real or artificial horizon and why motion cues can have a dramatic effect on controlling marginally stable plants (Shirley and Young 1968; Young 1967). The crossover model has been extended to multi-loop control and validated across a wide variety of plant dynamics and extensively applied in many domains, particularly in the area of vehicle handling quality standards (Young et al. 1973).

In the late 1960s, newer estimation and optimal control concepts, such as the Kalman observer and controller, were used to extend manual control theory. The optimal control model (Baron and Kleinman 1969) posited that the human observer's control strategy utilized an internal dynamic mental model for the plant, and it weighted feedback information based on prior knowledge of uncertainties. (Concurrent efforts by neuroscientists led to the present generation of Observer Theory models for orientation and sensory conflict in motion sickness described earlier.) Early applications included helicopter hovering and attention sharing. Results demonstrated the importance of vestibular motion cueing (Baron 1983; Curry et al. 1976).

When performing maneuvers such as flaring an aircraft on landing, a highly skilled human operator uses a "precognitive control strategy" and generates open loop, preprogrammed commands based on a mental model of the plant. The preprogrammed command accomplishes most of the maneuver, but the operator completes the task by switching back to conventional compensatory manual control for final error reduction. The Shuttle landing flare is an example of a task accomplished using precognitive control (Ashkenas et al. 1983). Landing performance depends critically on proper timing of the preprogrammed manual flare command and correct estimation of the aircraft state at that moment. Incorrect precognitive manual commands result in greater need for subsequent compensatory error reduction. After the flare, the pilot exerts "tight" control over aircraft altitude and altitude rate in order to achieve a smooth touchdown, employing relatively high control gain. Because the Shuttle flight control system has inherent phase delays and rate limits, excessively large pilot control gain can make the combined pilot-vehicle system unstable and trigger pilot induced oscillations (McRuer 1972). At the time it was not generally recognized that misperceptions of vehicle pitch attitude and rate could also potentially cause over control and pilot induced oscillations (PIO), but they were detected during the Shuttle Enterprise Approach and Landing Test flight test program, where disorientation was presumably not a factor. Since control system delays could not be eliminated, a stopgap solution was to detect large oscillatory control stick commands using a suitable nonlinear filter and adaptively reduce pilot control authority (Smith and Edwards 1980). Adaptively reducing control authority worked for "conventional" PIO. However, as described earlier, STS-3 subsequently experienced a PIO despite the PIO suppression filter. The only solution for disorientation induced PIO is to provide strong visual cues to pitch and pitch rate via a HUD and restricting landings to conditions of good visibility. If the Shuttle were required to land in brownout/grayout conditions (e.g. as are Lunar Landers), PIO would be a continuing concern.

Landing on a planetary body requires a number of operational tasks including identification of an appropriate location that is level and free of hazards while maintaining a stable controlled descent to the surface. Various sensorimotor challenges may interfere with crewmembers' performance. These include the astronauts' first exposure to partial gravity following microgravity adaptation, the unique vehicle motions experienced on decent, and dust blowback from the descent engine thruster that may obscure vision. Models of human spatial orientation perception have been developed that can be used to predict the potential for disorientation in partial gravity environments (Clark et al. 2015b). These models predict that spatial misperceptions are likely to occur during landings in partial gravity environments, particularly with limited or incomplete visual cues. For example, a powered descent acceleration profile creates the misperception that the landing vehicle is upright, even when the vehicle has a large pitch or roll angle. When full visual information is provided these perceptual illusions are largely suppressed; however, dust blowback during landing may obscure visual cues out the window and exacerbate spatial disorientation. These model predictions have been validated empirically using the NASA Ames Vertical Motion Simulator in which subjects self-reported their perceptions of vehicle motions during lunar-landing-like motions (Clark et al. 2014). Current research is focused on development of advanced display systems that could be implemented as countermeasures for landing spatial disorientation that include enhanced situation awareness displays and synthetic terrain displays that may help reduce potential landing misperceptions.

VI. RISK IN CONTEXT OF EXPLORATION MISSION OPERATIONAL SCENARIOS

A. Countermeasures and their effectiveness in mitigating risk

Most of the countermeasures to adverse effects of spaceflight on the human nervous system have been used to reduce space motion sickness (SMS). Prevention would be the best countermeasure, and the disruptive nature of SMS has led to a variety of approaches for preventing and controlling this malady. Unfortunately, only limited success has been achieved to date. Research in this area has proceeded along four broad lines of inquiry, namely selection screening, pharmacologic treatment, training, and the use of mechanical or electrical devices.

Attempts to prevent space motion sickness have included crew selection with a high tolerance to vestibular stimulation. Khilov (Khilov 1974) contended that the most suitable individuals should exhibit the smallest magnitude in response to various vestibular tests. Suitability can be further assessed by repeating these tests after administration of chloral hydrate, which removes the cortical inhibition of vestibular reactions. Applicants to the U.S. Astronaut Corps are not screened for motion sickness resistance. Although the Russian space program uses this process, it has been met with little success (Clément et al. 2001a; Lapayev and Vorobyev 1986). Moreover, crewmembers who have completed preflight Coriolis tests have shown no correlation between test tolerance and susceptibility to SMS (Reschke 1990).

1. Pharmacological Countermeasures

Many drugs have been tested for their effectiveness against motion sickness. Although some drugs have proven somewhat effective, no drug or drug combination has been identified that protects all individuals.

The mechanism(s) of action of the effective anti-motion sickness drugs is unclear, but it has been noted that the action(s) responsible for their anti-motion sickness efficacy tends to differ from the drug's primary action (Money 1970). Numerous studies have found scopolamine, an anticholinergic (parasympatholytic) drug, to be effective in treating motion sickness (Attias et al. 1987; Graybiel et al. 1981; Graybiel and Knepton 1977; Graybiel et al. 1976; Graybiel and Lackner 1987; Grigoriev et al. 1986; Homick et al. 1983; How et al. 1988; Karkishchenko 1989; Laitinen et al. 1981; Levy and Rapaport 1985; McCauley et al. 1979; Noy et al. 1984; Offenloch et al. 1986; Pyykko et al. 1985; Shashkov Vs Fau - Sabaev and Sabaev 1981; Shupak et al. 1989; van Marion et al. 1985; Wood and Graybiel 1968; Wood and Graybiel 1970; Wood and Graybiel 1972; Wood et al. 1986; Wood et al. 1987a; Woodard et al. 2014). Although most of the antihistamines tested for anti-motion sickness properties have had some benefit, they tend to be less effective than scopolamine. Promethazine, the most effective of the antihistamines, approaches scopolamine in efficacy (Wood and Graybiel 1972). The few sympatholytic drugs that are effective against motion sickness are of marginal benefit and have less effect than the least effective antihistamine (Wood and Graybiel 1968). The combination of a parasympatholytic drug (scopolamine) and a sympathomimetic has also been more effective than these classes of drugs taken alone.

Anti-motion sickness drug research has been reviewed by Wood (Wood 1979; Wood 1990). The vast majority of anti-motion sickness drugs have been given orally. However, the complications of oral medications force frequent dosing and the use of secondary medications via other routes of administration to overcome decreased absorption (Attias et al. 1987; Bagian 1991; Becker et al. 1984; Chess et al. 1975; Davis et al. 1993a; Davis et al. 1993b; Graybiel et al. 1981; Graybiel et al. 1976; Graybiel and Lackner 1987; Homick et al. 1983; How et al. 1988; Levy and Rapaport 1985; McCauley et al. 1979; Offenloch et al. 1986; Pyykko et al. 1985; Reason and Brand 1975; van Marion et al. 1985; Wood et al. 1987b). The occurrence of side effects also precludes the effective use of many of these drugs. Two newer classes of antiemetic drugs, 5HT3 and NK1 receptor antagonists, may be promising candidates for the treatment of motion sickness (Gardner et al. 1995; Koch et al. 1994; Stott et al. 1989).

In-Flight Medication

A reported 28–30% of all Shuttle crewmembers received medication for relief of SMS during flight (Santy and Bungo 1991). In the U.S. program, scopolamine, scopolamine with dextroamphetamine (scop-dex), promethazine, promethazine with ephedrine, metoclopramide, naloxone, and compazine have all been used to treat SMS with varying degrees of success (Bagian and Ward 1994; Davis et al. 1993a; Davis et al. 1993b; Graybiel 1980; Thornton et al. 1987b). Reports are available on the prophylactic and in-flight use of scop-dex taken orally (Davis et al. 1993a). Only 3 of 19 crewmembers who took this medication experienced no SMS symptoms.

Intramuscular (IM) promethazine has been used successfully to treat SMS symptoms. Davis et al. (Davis et al. 1993b) reported that of 20 crewmembers given 25–50 mg of promethazine IM (dose adjusted for body weight) on flight day 1, 25% were still classified as "sick" on the second flight day. In contrast, 50% of the 74 crewmembers reporting SMS on the first day of flight who did not receive promethazine, or received other anti-motion sickness medications, were still "sick" on flight day 2. Ninety percent of those who received IM promethazine reported relief from SMS symptoms within 1 to 2 hours of dosing and only three crewmembers needed a second dose. Three of the IM promethazine recipients reported drowsiness after administration, but the injection is often given immediately before the sleep period. An IM injection of 25–50 mg of promethazine is now the recommended treatment for moderate to severe cases of SMS in the U.S. space program; whereas oral and suppository routes are used for less severe symptoms. Some crewmembers have taken a prophylactic combination of promethazine and dextroamphetamine before launch. The success of IM promethazine administration is encouraging. Questions still remain, however, as to whether the effectiveness of promethazine is due to its pharmacologic effect or its route of administration (Bagian 1991).

One published study has investigated the effect of space flight on the pharmacokinetics of the stimulant dextroamphetamine and the anti-emetic scopolamine. In this study, there was a high level of inter-individual variability in the level of drug absorbed when compared with a similar drug administration regime dosed preflight on the ground. Although the sample size may be insufficient, the results illustrate the variability in absorption rate over time; this factor together with drug presentation may lead to variability in efficacy (Braddock 2017).

Currently, anti-emetic medications received by the astronauts before landing include meclizine, scopolamine, promethazine, and odensetron (Lee et al. 2020b). These medications are usually administered during the first 25-30 hours after landing. An intranasal formulation of scopolamine may allow for self-administration of medication during capsule wave motion (Stankovic et al. 2019).

The variable success of anti-motion sickness drugs administered during flight may be due to changes in drug absorption or metabolism by factors such as dehydration, reduced gastrointestinal motility, changes in body chemistry, changes in cabin pressure, and disruption of normal sleep/wake cycles. The concomitant administration of medications for other indications is another confounding factor (Santy and Bungo 1991; Wotring 2015).

Although anti-motion sickness drugs offer some protection, they may interfere with the adaptation process, and symptoms controlled by these drugs are experienced again once treatment ceases. This was observed for scopolamine, which resulted in a shift towards the use of promethazine. There have been anecdotal reports of medication usage prior to extravehicular activities with concerns about cognitive and performance side effects associated with this usage.

2. Mechanical Devices and Stimulation

To reduce or prevent cephalad fluid shifts, the Soyuz-38 crew wore a pneumatic occlusion cuff on the hips. The cuff, worn for 20 to 30 minutes at -40 to -60 mmHg, reportedly decreased or eliminated dizziness, illusions, nausea, and the sensation of head pulsation (Gorgiladze and Brianov 1989; Matsnev et al. 1983). Several mechanical countermeasures are under investigation to reduce headward fluid shifts, including lower body negative pressure (LBNP), venoconstrictive thigh cuffs, and an impedance threshold device resistive inspiratory breathing (Marshall-Goebel et al. 2021b). LBNP during spaceflight may alter the ocular venous system, as evidenced by a decrease in intraocular pressure (Greenwald et al. 2021), and reduce the associated flow and tissue disturbances at the neck and splanchnic levels (Arbeille et al. 2021).

The neck pneumatic shock absorber (NPSA) device, a cap with rubber cords that provide a load to the cervical vertebrae and neck muscles, stretches the user's neck muscles to maintain an erect head position and to restrain any turning or tilting of the head (Matsnev et al. 1983). The NPSA was designed to be worn during working hours for the first 3 or 4 days of a mission. It was used on the Soyuz-T3, -49, -40, and T-7 spacecrafts as well as on the Salyut-6 and -7 orbital stations. Cosmonauts reported the NPSA to be effective in alleviating dizziness, illusions, discomfort, and nausea with no adverse effect on performance (Matveyev 1987). This was attributed to "normalization of the vestibulocervical reflex system". However, head movements, which are known to provoke SMS symptoms, were limited by this device.

Various hardware solutions have been proposed to stimulate the vestibular system, augment vestibular cues, or enhance vestibular cues, though none of these are currently routinely used by NASA astronauts. For example, mechanical stimulation of the soles of the feet has been proposed as a neuromotor countermeasure (Layne et al. 1998a). Load suits, including the Penguin Suit (Kozlovskaya and Grigoriev 2004), the Gravity Loading Countermeasure Skinsuit (GLCS) (Carvil et al. 2017), and the Variable Vector Countermeasure Suit (V2Suit) (Duda et al. 2015), have been proposed to mimic the mechanical loading to the body (but obviously not the vestibular system) normally experienced on Earth, which may help as an adjunct to exercise for maintaining motor control coordination.

3. Stroboscopic Goggles

Motion sickness in the general population is a significant problem driven by increasingly sophisticated modes of transportation, visual displays, and virtual-reality environments. As such, it is important to investigate nonpharmacological alternatives for the prevention of motion sickness for individuals who cannot tolerate the available anti-motion sickness drugs, or who are precluded from medication because of operational environments. Both NASA and the U.S. Army have been investigating stroboscopic vision as a way to provide a simple and easily managed treatment for motion sickness (Reschke et al. 2006). Specifically, a five-part study was designed to investigate the effect of stroboscopic vision (either with a strobe light or liquid crystal display (LCD) shutter glasses) on motion sickness while (1) using visual field reversal; (2) reading while riding in a car (with or without external vision present); (3) making large pitch head movements during the 0 g phase of parabolic flight; (4) exposed to rough seas in a small boat; and (5) seated and reading in the cabin area of a UH60 Black Hawk helicopter during provocative flight patterns. A total of 69 subjects participated in selected phases of the study. Fewer subjects suffered from motion sickness under stroboscopic conditions. Stroboscopic illumination prevents retinal slip, thereby treating motion sickness symptoms. Shutter glasses with a cycle frequency of 4 or 8 Hz and a short dwell (glasses clear) time (10–20 ms) are as effective as a strobe light, producing a useful adaptation during either self- or surround-motion without the consequences of using disabling MS drugs (Reschke et al. 2007a).

4. Electrical Devices

The use of weak electrical currents also has been explored to prevent or treat motion sickness. Electroanalgesia or electrotranquilization involves the use of two electrodes with one placed on the forehead and one on the mastoid process. Melnik et al. (Melnik et al. 1985) increased the current until the subject reported a sensation of warmth in the area of the electrodes; sessions lasted 30 to 60 minutes. Nekhayev et al. (Nekhaev et al. 1986) and Polyakov (Poliakov 1987) incorporated a pulsed current during sessions lasting an hour. Electroanalgesia did not increase resistance to experiment-induced motion sickness when sessions were performed before stressful motion. However, sessions conducted between two motion-stressor tests reduced or eliminated the residual symptoms from the first test and increased tolerance to the test performed after the electroanalgesia session. A second electroanalgesia session after the second motion-stressor test also improved recovery from symptoms induced by that test. No undesirable side effects were reported.

Ivanov & Snitko (Ivanov and Snitko 1985) observed that motion sickness affected conductivity alongside standard acupuncture pathways regardless of symptom severity. Electro-acupuncture was used successfully by this group to treat seasickness. Others have found electrical acustimulation and acupressure to be effective in reducing vection-induced nausea (Hu et al. 1992; Hu et al. 1995). Acustimulation may work by enhancing the normal slow-wave myoelectrical activity of the stomach (Lin et al. 1997). Sub-threshold multichannel electrical stimulation of the antigravity cervical muscles also was reported to be promising as a countermeasure against motion sickness (Matveyev 1987).

Although electrical devices are reported to be effective in counteracting terrestrial motion sickness, they have not been tested in the space environment. Data obtained from in-flight questionnaires indicated that all the mechanical devices used in-flight improved how the cosmonauts felt and also led to the attenuation of illusions to some extent. Of these, the NPSA was reported to be the most effective. Sleep and the performance of demanding work tasks, which distracted the cosmonauts from the unpleasant sensations, also decreased symptoms of discomfort (Bryanov et al. 1986; Kornilova 1995).

Minor and Goldberg (1991) had previously noted that galvanic anodal (inhibitory) currents, when delivered bilaterally, results in a reversible ablation of irregular afferents. Irregular afferents are important for encoding self-motion, and Oman and Cullen (2014) have speculated “sensory conflict” neurons may exist in “reafference” neural processing associated with active motion. Galvanic vestibular reduction (GVR) may therefore be attempted through either a cancellation-type feedback of actual motion (Peterka 2012) or by delivering bilateral inhibitory signals provided independent of sensing actual motion (Minor and Goldberg 1991). Recent studies have measured a reduction in motion sickness symptoms and changes in electrogastrography in the GVR treatment group relative to controls (Cevette et al. 2014). In this paradigm, the subject's only external visual cues were presented through a virtual window where both the window and subject were misaligned with the vehicle direction. Current research is exploring GVR for capsule wave motion applications.

5. Vestibular Desensitization Training

Vestibular training has been used in attempts to prevent or control the symptoms of SMS. Vestibular training techniques investigated thus far have been based on one of two suppositions: (a) adaptation to stressful motion can be hastened through previous exposure to conflicting sensory inputs or (b) symptoms can be avoided by learned control of autonomic responses.

Lapayev and Vorobyev (Lapayev and Vorobyev 1986) hypothesized that motion sickness susceptibility is proportional to the ratio of signals from the vestibular system and other sensory (e.g., visual, proprioceptive) systems. They propose that the most effective method of increasing tolerance to motion sickness is to train the vestibular system while stimulating the other senses. The Russian space program primarily uses Coriolis and cross-coupled angular acceleration as preflight vestibular training. However, this method does not duplicate the sensory conflicts or fluid shifts encountered in weightlessness. Aizikov et al. (Aizikov et al. 1991) observed that using a predetermined sequence of muscle tension and relaxation increased tolerance to experimentally induced motion sickness by reducing the number of symptoms and shortening the recovery time. These investigators theorize that the afferent propriotactile information generated by the muscle-tension regimen provides enough information on body position to override coincident, possibly inaccurate, vestibular information.

6. Preflight Adaptation Training (PAT)

Preflight adaptation training is based on the following postulates: (a) that microgravity rearranges sensory stimuli and astronauts adapt to the rearranged stimuli (sensory conflict theory); (b) that adaptation may result from sensory compensation, reinterpretation of stimuli, or both (sensory compensation and OTTR hypotheses); and (c) that people can learn and store perceptual, sensory, and sensorimotor responses appropriate to different sensory stimulus conditions and can learn to invoke these alternative responses when necessary (Harm and Parker 1993).

Two training devices are used to provide a variety of stimulus rearrangements and train sensorimotor reflexes: the device for orientation and motion environments (DOME) that achieves graviceptor stabilization and the tilt-translation device (TTD) that produces graviceptor-visual rearrangement. Theoretically, training with these devices would produce the necessary responses to weightlessness and for the return to a 1-g environment, such as compensatory eye movements, postural-muscle reflexes, and self-motion and orientation experiences in relation to visual scene movements.

Ground-based studies using the TTD trainer have revealed that a 270° phase relation between tilt and surround-motion in the TTD best supports reinterpretation of otolith signals as linear translation (Harm and Parker 1993; Harm and Parker 1994; Reschke et al. 1988). Exposure to this profile also results in decreased compensatory eye movement gain, net gaze compensation, and decreased postural stability (Harm et al. 1991; Harm and Parker 1993; Michaud et al. 1989; Paloski et al. 1990). These results are consistent with the OTTR model of sensory adaptation and are consistent with observations of astronauts and cosmonauts during or after flight. Flight investigations involving these training devices focused on providing an experience of sensory rearrangement that results in illusions of linear or angular self- or surround-motion. The primary purpose of these studies was to teach astronauts to describe perceptual phenomena systematically by using a quantitative "motion perception vocabulary" related to anatomy and physiology so that they can properly describe perceptual illusions.

Post-flight training on the TTD has provided evidence that the simulated perceptual experiences are similar to those experienced in-flight. SMS symptoms and visual disturbances have been re-elicited, and perceptual illusions of linear self-motion and tilt angle are intensified relative to preflight stimulation (Harm and Parker 1993; Harm et al. 1999). These results generally support the OTTR model of sensory adaptation to microgravity and suggest that the training devices can simulate the appropriate sensory rearrangements. Moreover, crewmembers who participated in this study showed an average 33.5% improvement in SMS symptoms compared with those who did not participate (Harm et al. 1999).

7. Sensorimotor Adaptability Training

A comprehensive sensorimotor adaptability (SA) training program has been proposed as a countermeasure to facilitate rapid adaptation to novel gravitational environments and readaptation to Earth's gravity (Bloomberg et al. 2015b). The human brain is highly adaptable, enabling individuals to modify their behavior to match the prevailing environment. It has been previously shown that subjects trained to adapt to varied sensorimotor challenges can adapt faster to new sensory environments that they have never experienced before (Cohen et al. 2005b; Mulavara et al. 2009; Roller et al. 2009; Roller et al. 2001; Seidler et al. 2006). This is a process known as adaptive generalization that allows you to enhance the ability to "learn how to learn" to adapt to novel environments (Bloomberg et al. 2015b; Krakauer 2006; Seidler 2010).

By applying these motor-learning concepts for training astronauts these programs can enhance the individual's ability to rapidly adapt behavioral responses following a gravitational transition. To minimize cost and demands on crew time, current training concepts involve integrated SA training with existing exercise activities, namely treadmill walking. The SA training program being developed entails manipulating the sensory conditions of treadmill exercise to systematically and simultaneously challenge multiple sensorimotor systems while conducting nominal exercise activities. To provide SA training, investigators have mounted a treadmill on a six degree-of-freedom motion base to produce variation in the support surface offering subjects balance challenges during walking (Brady et al. 2009; Peters et al. 2012a; Peters et al. 2013). Additional sensorimotor challenges are provided by exposing subjects to variation in visual input during walking using a projected virtual scene that produces variation in visual flow

(Brady et al. 2012; Buccello-Stout et al. 2008; Mulavara et al. 2005b; Nomura et al. 2005; Richards et al. 2004; Richards et al. 2007).

Bloomberg et al. (Bloomberg et al. 2015b) have reviewed several studies showing that subjects who received SA training adapted faster than controls when presented with a novel discordant sensory environment because they were able to apply adaptive skills that were learned during their earlier training sessions. Importantly, the training improved performance across a number of modalities including enhanced locomotor function and increased multi-tasking capability when walking in a novel, discordant sensory environment not previously experienced by the subjects. This improved performance could be retained over a 6-month period and perhaps longer, indicating that a component of this training could take place before long-duration missions (Batson et al. 2011).

A recent study collected functional MRI data while participants performed a manual adaptation task during four separate test sessions over a three-month period (Ruitenberg et al. 2018). Participants exhibited reliable retention of adaptation across the four sessions changes in neural activation that occur over the time course of multiple days of sensorimotor adaptation. Preflight adaptability training could play a central role in facilitating crewmember adaptive response to new gravitational environments in support of both short and long-duration spaceflight. Given that training may be retained for many months, preflight training countermeasures would probably be sufficient to increase adaptability, even for long-duration flight. Therefore, one can conceive of this training more in terms of a preflight “inoculation” that will not require significant amounts of crew time preflight and may only require infrequent “booster” training to maintain the training effect. Finally, a collateral benefit of the application VR technology, in this context, will be to make training programs more interesting, ultimately leading to increased adherence to prescribed training regimens.

8. Biofeedback Training

The autonomic nervous system initially responds to motion-induced stress through sympathetic activation followed by parasympathetic activation. If nausea and vomiting are parasympathetic reactions to sympathetic activation, then motion sickness symptoms might be prevented by training an individual to maintain autonomic regulation at baseline (Cowings et al. 1986).

Autogenic feedback training (AFT) combines cognitive imagery and body exercises to produce a desired change in autonomic activity. Sensory feedback regarding information about selected autonomic activities is provided to the subject through visual or auditory cues (Cowings 1990). Two crewmembers in the U.S. Shuttle program performed AFT before flight and two other crewmembers on the same flight served as untrained controls. During flight, the crewmember who showed mixed success in achieving autonomic control during training experienced one severe episode of SMS. Limited spaceflight testing showed that a crewmember exhibiting greater autonomic control during training before flight reported no severe symptoms. Two untrained crewmembers had multiple episodes of severe symptoms despite the administration of anti-motion sickness drugs (Cowings 1990).

More recently, a test was conducted in subjects who received 2 hours of autogenic feedback training before being exposed to the same accelerations of the Orion crew vehicle during re-entry. These subjects had significantly lower motion sickness symptom scores when compared to controls who did not receive the feedback training (Cowings et al. 2018).

Because AFT does not change the perception of vestibular stimulation, this type of training must interrupt the autonomic response after the sensory conflict has already occurred. Therefore, AFT and parasympatholytic drugs like scopolamine may achieve the same effect but through different mechanisms. AFT reduces sympathetic activity, thereby eliminating the parasympathetic reaction and its resultant symptoms. Scopolamine reduces the parasympathetic response to the increased sympathetic activity that has already occurred (Cowings et al. 1986).

9. Enhancing In-Flight Exercise with Sensorimotor Training

Physical exercise has been a critical component of countermeasures for long-duration flights (English et al. 2020). The ISS exercise program consists of both resistive and aerobic exercise. Aerobic exercise has been performed on both the Treadmill Vibration Isolation System (TVIS) and the Cycle Ergometer with Vibration Isolation System (CEVIS) and now more recently using the Combined Operational Load Bearing External Resistance Treadmill (COLBERT or T2). For resistive exercise the interim Resistive Exercise Device (iRED) was initially implemented on the ISS, but this system had some limitations including limited loading and resistance that was notnot constant. This was replaced by the Advanced Resistive Exercise Device (ARED) that utilizes vacuum cylinders and inertial flywheels to simulate constant mass and inertia of free weight exercise and provides twice the loading of the iRED. In addition to attenuating loss of bone mineral density and muscle mass (Smith et al. 2012) crewmembers that exercised on the ARED also had less decrement in postflight postural stability and agility scores compared to subjects using the iRED (Wood et al. 2011). The increased body loading during ARED exercises may have provided greater postural challenges during exercise improving postflight balance performance.

Importantly, exploration missions will impose new restrictions on in-flight exercise capabilities compared to the ISS. For example, there are currently no in-flight treadmill designs that fit the volume or stabilization constraints of exploration vehicles. In addition to aerobic conditioning, treadmill running onboard the ISS is thought to provide a sensorimotor stimulus through dynamic postural challenges requiring single-limb segmental coordination in response to axial body loading (English et al. 2020). Treadmill running also engages the central pattern generator to rehearse rhythmic motor outputs that produce periodic sensory input (e.g. proprioceptive stretch and foot tactile inputs) such as that required for the control of terrestrial locomotion. These cumulative stimuli may have an essential sensorimotor training effect for maintaining post-flight posture and locomotion.

Data from spaceflight and from analog studies collectively suggest that body unloading decreases the utilization of proprioceptive input, and this adaptation strongly contributes to balance dysfunction after spaceflight. For example, on return to Earth, an astronaut's vestibular input may be compromised by adaptation to microgravity, but their proprioceptive input is compromised by body unloading. Since proprioceptive and tactile input are important for maintaining postural control, keeping these systems conditioned and adaptable to respond to upright balance challenges during flight may improve functional task performance after flight through dynamic reweighting of sensory input (Macaulay et al. 2021).

One approach involves keeping the proprioceptive and tactile systems reliable enough to overcome transient vestibular deficiencies for functional task performance upon return to a gravitational environment. The four promising modalities identified for inclusion in such a countermeasure include (a) axial body loading (Marchant et al. 2020); (b) postural/proprioceptive challenges (Bakkum et al. 2020); (c) tactile input (Reschke et al. 2009); and (d) and sensory feedback (Sienko et al. 2018). Integrating these modalities with other countermeasures (such as Low Body Negative Pressure, LBNP) may increase the efficiency of risk mitigation strategies and have additional indirect benefits. In terms of training schedule, some data suggest that undulated training approaches utilizing variable postural challenges and conditions of feedback may enhance the benefits for adapting to novel sensorimotor environments (Bloomberg et al. 2015b).

However, these studies have not been conducted during spaceflight or spaceflight analogs. Therefore, future investigations are warranted to determine the optimal training parameters given individual differences in proprioceptive utilization (Seidler et al. 2015). A successful countermeasure might also translate to ground-based balance training interventions and assessments. Older adults and various clinical populations known to experience declining proprioceptive function may benefit from similar training methods on Earth (Aman et al. 2015; Oddsson et al. 2015). Thus, the development of an inflight proprioceptive countermeasure may have widespread impact on our understanding of balance control and the mitigation of fall risks.

10. Self-administered Balance Rehabilitation

The process of readapting to Earth's gravity may be facilitated at the time of reentry when crewmembers perform systematic head movements. Because of operational constraints, scientific study at this time has not been possible, but anecdotal reports from Shuttle crewmembers have indicated that performing head movements that slowly increase in amplitude can minimize motion illusions and motion sickness. The head movements were performed in the yaw plane initially then in the pitch and/or roll planes, using progressively larger head tilts. Each crewmember should only perform movements at amplitudes and rates that can be tolerated at the time, but crewmembers should not restrict head movements too much or they may have problems when they must move to exit the spacecraft. The configuration of crewmembers in the Soyuz at landing, the volume of the spacecraft, and the higher G profile makes moving the head systematically more difficult than it was in the Shuttle; however, making systematic head movements during and after reentry is still recommended to crewmembers.

Vestibular rehabilitation therapy (VRT) is a type of balance rehabilitation therapy. It includes specific exercises that can eliminate or significantly reduce symptoms by promoting CNS compensation for inner-ear deficits. The program is designed to achieve multiple goals: (a) decrease dizziness and visual symptoms; (b) increase balance and walking functions; and (c) increase general activity levels. The program may include exercises for (a) coordinating eye and head movements; (b) stimulating the symptoms of dizziness in order to desensitize the vestibular system; (c) improving balance and walking ability; and (d) improving fitness and endurance. Exercises vary depending on the type of symptoms. Balance retraining exercises are designed to achieve steadier walking and standing through improvements in coordination of muscle responses and organization of sensory information (e.g., vision, proprioception). Such treatment is part of the "post-flight reconditioning" of astronauts for 2 hours each day after long-duration spaceflight. Reconditioning specialists supervise individualized post-flight reconditioning activities, adjusting the level of task difficulty according to the crewmember's level of balance recovery. Most of the activities benefit many body systems even if they target specific functions (Wood et al. 2011).

The exercises selected for post-flight reconditioning are based on activities of daily living that crewmembers have reported to be challenging, such as bending over to pick up an object, stooping down to tie one's shoes, and tilting the head backward. Signs of sensorimotor deconditioning are making wide turns, having difficulty changing direction, and making deliberate and slow motions that involve coordination of body segments. Slowed reaction times, difficulty in judging distances, and misperception of force also impair crewmembers' abilities to perform their normal activities.

Post-flight reconditioning activities progress from lower risk to higher risk and simple to complex as crewmembers master particular skills and as particular movements become less provocative. Some exercises are performed every day and others are performed every other day. Posture and stability exercises are performed every day while standing. They include head movements in different planes, toe touches followed by hyperextensions, and trunk twists. Standing with both legs on a stable surface progresses to standing on one leg and standing on an unstable surface. Because mobility facilitates the resolution of sensorimotor symptoms after spaceflight, astronauts are encouraged to walk as much as possible, beginning on landing day. The limits of the individual's motion tolerance are continually challenged; a "walking toe touch" is one of the most provocative activities. Some activities involve catching and throwing balls of increasing weight, sometimes while walking or shuffling.

Reconditioning specialists and flight surgeons use quantitative measures to evaluate post-flight recovery of each crewmember. Posture is assessed by computerized dynamic and sensory organization tests, including some performed with dynamic pitch head tilts (Wood et al. 2015). Agility is measured by testing crewmembers' ability to move forward, backward, and to either side around cones on the floor. Preflight and post-flight tests of posture and agility are used to measure the effectiveness of countermeasures such as in-flight exercise.

11. Spatial Orientation Aids

Several spatial orientation aids have been proposed to improve spatial orientation and manual control performance. As described above, vibrotactile feedback has been used to improve spatial awareness during passive inflight motion (van Erp and van Veen 2006). The use of a tactile spatial awareness system (TSAS) has also improved manual control performance during post-flight testing. During the closed-loop nulling task, small tactors placed around the torso vibrated according to the actual body tilt angle relative to gravity. Performance on the closed-loop tilt control task improved with the tactile display feedback of tilt orientation during both pre- and post-flight testing. In fact, with the TSAS, the performance during early post-flight tests was comparable to that without TSAS during the preflight tests (Clément et al. 2018; Clément and Wood 2014). In ground-based studies, vibrotactile sensory augmentation has also proven beneficial on balance performance among people with vestibular disorders (Bao et al. 2019; Lackner 2021). Current research is also examining similar approaches using either actual or virtual presentations of Earth-fixed visual references that may mitigate motion sickness during capsule wave motion.

12. Just-in-time trainers

As mission duration increases, lack of training retention is expected to negatively impact operator performance of complex tasks (Dempsey and Barshi 2021; Foale et al. 2005). This risk may be exacerbated during periods of G-transitions since vestibular alterations can impact attention and cognitive processing ability (Bigelow and Agrawal 2015), especially related to spatial memory (Smith 2021). While experimental evidence for cognitive deficits during spaceflight is somewhat equivocal (Manzey 2017), dual-task/divided-attention paradigms have been more sensitive to change (Strangman et al. 2014). There are a number of stressors during spaceflight that impact cognitive processing (Stahn and Kuhn 2021); however, cognitive overload may be higher when complex motor skills are required around periods of greater adaptative change (Bock et al. 2010). An example is the decrements in dual-tasking described above in Section V.A.3 (e.g., Moore et al. 2019).

Decrements in dual-tasking may be related to alterations in time perception during G-transitions (Clément 2018). This “time compression” may result from either loss of task proficiency or lack of cognitive reserve. The "Portable In-flight Landing Operations Trainer" (PILOT) was a laptop computer simulator that was flown as a tool for helping the mission commander and pilot maintain their proficiency for approach and landing during longer duration Space Shuttle flights (Kennedy et al. 1997; Life Science Data Archive 2020). One Shuttle commander who experienced vertigo during the landing (personal communication) attributed the “just-in-time” training of the PILOT to be able to lower perceived cognitive workload and effectively pilot through disorientation to complete a successful landing. The success of the Shuttle PILOT serves as a basis for our proposed “just-in-time” training countermeasure to mitigate risks associated with spatial disorientation during lunar landings by maintaining peak crew task training proficiency (see recommendation #6, p. 22 in NASA Flight Safety Office 2013). While the fidelity of the inflight laptop trainers is limited, for the purpose of maintaining task proficiency, the Shuttle PILOT was highly effective.

Similar JIT trainers and research platforms have been used for landing and telerobotic controls by the Russian space agency (e.g., Pilot-T experiment, Bubeev et al. 2019). During the pilot-T experiment, performance over just 6 sessions (approximately once per month) was sufficient to *increase* task proficiency and was not different than using twice as many sessions over the mission (Schastlivtceva et al. 2021). Another example is the telerobotics platform that has been developed, in fact, for just-in-time (JIT) training on the Canadarm2 track-and-capture activities (Ivkovic et al. 2019).

13. Spatial Disorientation Training

Galvanic Vestibular Stimulation (GVS) entails electrical stimulation to the vestibular labyrinth via surface electrodes placed over the mastoid bones that pass small currents, activating primary vestibular afferents. It has been used to stimulate the vestibular labyrinth artificially for laboratory studies of human vestibular cortex, spatial orientation, postural control, and locomotion (Moore et al. 2011; Moore et al. 2015). GVS produces behavioral changes in balance function, gaze, head-trunk coordination, and locomotor disturbances that are similar to those observed in post-flight astronauts (Moore et al. 2006). GVS has been validated in the Vertical Motion Simulator at NASA Ames Research Center during high-fidelity Shuttle landing simulations. When exposed to GVS, pilot subjects (including a veteran shuttle commander of 3 flights) experienced spatial disorientation and subsequent decrements in landing performance equivalent to that observed in actual Shuttle landings (Moore et al. 2011). The GVS analog accurately reproduces the effects of microgravity exposure on the central nervous system and might be used to improve training of astronauts for future long-duration missions (Dilda et al. 2014).

Dilda et al. *(Dilda et al. 2014)* have also shown that subjects exhibit central adaptation phenomenon with repeated GVS exposure in a study of normal subjects for an extended period of up to 12 weeks (120 min of total exposure). During each trial subjects performed computerized dynamic posturography, and eye movements were measured using digital video-oculography. Follow up tests were conducted 6 weeks and 6 months after the 12-week adaptation period. Postural performance was significantly impaired during GVS at first exposure but recovered to baseline over a period of 7–8 weeks (70–80 min GVS exposure). This postural recovery was maintained 6 months after adaptation. In contrast, the roll vestibulo-ocular reflex response to GVS was not attenuated by repeated exposure. This suggests that GVS adaptation did not occur at the vestibular end organs or involve changes in low-level (brainstem-mediated) vestibulo-ocular or vestibulo-spinal reflexes. Faced with unreliable vestibular input, the cerebellum reweighted sensory input to emphasize veridical extra-vestibular information, such as somatosensation, vision, and visceral stretch receptors, to regain postural function. After a period of recovery subjects exhibited dual adaption and the ability to rapidly switch between the perturbed (GVS) and natural vestibular state for up to 6 months. In a follow up study, Moore et al. (Moore et al. 2015) found that pre-adaptation to GVS is associated with enhanced sensorimotor performance in a flight simulator when asked to null the roll motion of a visual bar presented on a screen using a joystick compared to subjects who were not adapted to GVS. Thus, GVS may be used as a training modality to enhance adaptability to aid recovery after spaceflight (Dilda et al. 2014; Moore et al. 2015).

14. Imperceptible Electrical Stimulation

A general phenomenon is that paradoxically if noise is added to neural sensory systems, their ability to detect sub-threshold signals improves, a mechanism termed Stochastic Resonance (SR). SR thus enables the enhanced detection of relevant sensory signals. SR can be thought of simply as "noise benefit" by increasing information transfer in the presence of non-zero level of noise (for reviews see (Aihara et al. 2010; Collins et al. 2003; McDonnell and Abbott 2009; Moss et al. 2004)). SR has been observed in human hearing (Jaramillo and

Wiesenfeld 1998; Ward et al. 2002; Zeng et al. 2000) and has been identified as an important component in cochlear coding strategy (Morse and Evans 1996). The presence of stochastic noise to sensory input has been shown to improve visual contrast sensitivity and detection (Simonotto et al. 1997; Ward et al. 2002); the degree of association between the heart rate responses and weak periodic oscillatory variation in central venous pressure (Soma et al. 2003); letter recognition (Piana et al. 2000); perception of ambiguous figures (Riani and Simonotto 1994); and visual depth perception (Ditzinger et al. 2000). SR in tactile sensation has been demonstrated in the response to weak mechanical stimuli (Collins et al. 1997; Collins et al. 1996a; Collins et al. 1996b; Ivey et al. 1998; Richardson et al. 1998). The application of mechanical noise to the feet has been shown to improve balance control through the reduction of sway in young and elderly subjects (Priplata et al. 2002; Priplata et al. 2003), as well as in patients with diabetes, those who have suffered a stroke (Priplata et al. 2006), and patients with functional ankle joint instabilities (Ross and Guskiewicz 2006; Ross et al. 2013). Similarly, balance improvement has been demonstrated with electrical noise applied to the back of the knee (Gravelle et al. 2002). Vibratory noise applied to the fingertip also enhanced balance performance based on SR phenomenon (Magalhaes and Kohn 2011). These same authors have also shown that the application of imperceptible electrical noise to the triceps surae during a force fluctuations, which were correlated to subsequent reductions in postural sway during quiet stance (Magalhaes and Kohn 2012). There have been a few studies that showed the effectiveness of applying sub-sensory vibratory noise to the soles of the feet during over-ground walking comparing elderly population with young control subjects (Galica et al. 2009). In a follow-up study, this group also showed the effectiveness of applying sub-sensory vibratory noise to the soles of the feet during treadmill walking in a set of control subjects (Stephen et al. 2012). SR using white noise based electrical stimulation at imperceptible amplitudes (at or below peri-threshold levels) of the vestibular system, applied using surface electrodes on the mastoid, leads to significantly improved balance and locomotor performance during periods of novel sensory challenges in healthy individuals and in Parkinson disease patients (Goel et al. 2015; Mulavara et al. 2011; Mulavara et al. 2015; Samoudi et al. 2015; Temple et al. 2018).

The methodology of using sub-threshold electrical stimulation of the vestibular system or similar stimulation of the proprioceptive systems at the sole of the feet will help retain and enhance the use of vestibular or proprioceptive information in performance of specific functions. Studies in the literature have investigated the usefulness of SR in conjunction with traditional training paradigms to improve performance (Ross 2007; Ross et al. 2007; Ross and Guskiewicz 2006; Ross et al. 2013). These investigators have shown significant improvement in postural balance control aiding recovery when electrical or mechanical SR stimulation to the muscles across the ankle joints was given in conjunction with conventional coordination training compared to training alone (Ross 2007; Ross et al. 2007; Ross and Guskiewicz 2006; Ross et al. 2013). Therefore, in general an individualized sensorimotor training program in conjunction with SR designed to promote the use of multiple sensory modalities can enhance the ability to adapt postural control and walking stability when exposed to a novel discordant sensory environment in the astronaut population. Given the individual variability of GVS sensitivity, it may be important to customize the stimulus amplitude levels for each individual to ensure the stimulation is optimized (Goel et al. 2019).

Age-related loss of vestibular function can result in decrements in gaze stabilization and increased fall risk in the elderly (Bermudez Rey et al. 2016; Noohi et al. 2020). One study was designed to see if low levels of electrical stochastic noise applied transcutaneously to the vestibular system can improve a gaze stabilization reflex in young and elderly subject groups (Serrador et al. 2018). Ocular counter-rolling (OCR) obtained in 16 subjects during low frequency passive roll tilts with imperceptible stochastic noise significantly increased OCR in the elderly. Since stimulation was effective at low levels undetectable to subjects, stochastic noise may provide a new treatment alternative to enhance vestibular function, specifically otolith-ocular reflexes, in the elderly or astronaut populations with reduced otolith-ocular function**.**

15. Artificial Gravity

Sensorimotor performance, as well as bone loss, muscle weakening, and cardiovascular deconditioning, among other deficits, are all known impacts of microgravity. The longer the flight duration, the more serious the health consequences become (Clément 2011). The current countermeasures on board the ISS (exercise, pharmaceutics, food complements) address each of these physiological systems in a piece-meal fashion. Artificial gravity, i.e., a sustained centripetal acceleration generated by centrifugation, represents a novel and integrated approach to addressing the detrimental effects of reduced gravity on the human body (Clément and Bukley 2007). All body systems are challenged simultaneously by its application, not simply one physiological system at a time. In addition, artificial gravity is an improvement upon the current ISS countermeasures as it addresses the root causes of the deconditioning phenomenon instead of treating its end-effects system-by-system as the current countermeasures do.

More recently, a special focus of concern is the deficit in vision acuity in astronauts on board the ISS, which is hypothesized to be caused by weightlessness-induced fluid shifts to the upper body leading to intracranial hypertension (Mader et al. 2011). If this hypothesis is confirmed, it could be an impediment for future long-duration deep space missions. Thus, an effective countermeasure against these effects will be required. Because it enables re-establishing g-induced hydrostatic gradients, centrifugation might be the most efficient countermeasure.

Generating centrifugal force equivalent to the gravitational force on Earth during long-duration exploration missions can be obtained by rotating the entire spacecraft. However, this solution is costly in terms of power and mass, and it creates issues with navigation and control, communication, and docking. Another, more affordable solution, is to rotate only one part of the spacecraft, or to utilize an on-board human centrifuge.

To help inform the final decision on whether to conduct continuous spin of the whole space vehicle or to intermittently expose the crewmember to short-radius centrifugation, the limits of human adaptation in a rotating environment must be revisited. We need to identify the acceptable and/or optimal ranges for radius and rotation rate to avoid unacceptable crew health and performance consequences (Arya et al. 2007; Fong et al. 2007; Lackner and DiZio 2005a; Reinertson et al. 2007; Symons et al. 2009; Warren et al. 2007; Zwart et al. 2009). For intermittent applications, we need to identify what level, duration, frequency, and time of day of exposure to artificial gravity are optimal (Young and Paloski 2007). We also need to investigate the physiological responses to transitions between artificial gravity, microgravity, and Moon or Mars gravity because such studies would be useful in assessing whether dual adaptation to a rotating and a non-rotating environment is possible (Lackner and DiZio 2003).

NASA and other space agencies are working on a global research program on artificial gravity that would leverage the facilities available around the world (e.g., short- and long-radius centrifuges, slow rotating rooms, bed rest/dry immersion facilities, suspension systems, etc.) and integrate studies on human, animal, and cell models. Standardization of measures performed before and after each artificial gravity intervention will allow for more compatible assessment across various studies. The biomedical measurements will focus on countermeasure validation, medical events, and subject acceptance and comfort (Clément 2017).

Regarding sensorimotor performance, artificial gravity projects that could be performed in the near future include the following: (a) test gravity level values along Gz within the range from microgravity to 1 g, using the methods described above, to reasonably reach conclusions on the threshold, optimal stimulus-response, and saturation for the effects of centrifugation on sensorimotor performance; (b) test the effects of gravity levels higher than 1 g to assess whether increasing the intensity of the Gz stimulus actually reduces the time of exposure needed; (c) compare whether exposure to centrifugation for intermittent, short periods of time in one or multiple sessions is as beneficial as continuous exposure to Earth's gravity; (d) investigate whether Gz centrifugation reduces intracranial pressure and possibly mitigates the visual impairment due to intracranial pressure (VIIP) syndrome; (e) assess whether centrifugation can possibly mitigate post-flight decrease in performance by studying the effect of centrifugation on cognitive and functional tasks; and (f) assess the effects of gravity gradient on spatial orientation by comparing the responses in subjects placed at various distances from the axis of rotation on a long radius centrifuge (Clément et al. 2015b).

Recent ground-based studies with subjects exposed to short-radius centrifugation along with exercise on cycle ergometer have shown that AG training was more effective in men than women (Evans et al. 2018) and more effective in subjects who exercised during AG than in those who passively rode the centrifuge (Diaz-Artiles et al. 2018).

In animals, one group of mice was exposed to continuous 1 g centrifugation on the ISS, while another group of mice remained exposed solely to weightlessness (Shiba et al. 2017). Results revealed that artificial gravity provides some protection from the spaceflight-induced increases in apoptosis of retinal cells and changes expression of proteins related to cellular structure, bone, and muscle mass (Tominari et al. 2019), immune response (Horie et al. 2019), and metabolic function (Mao et al. 2018).

B. Operational perspective on the risk

1. Sensorimotor Standard

A sensorimotor standard has been drafted (NASA Standard 3001) for exploration class missions: "*Pre-flight sensorimotor functioning shall be assessed and be within normal values for age and sex of the astronaut population. In-flight Fitness-for-Duty standards shall be guided by the nature of mission-associated high-risk activities. In-flight Fitness-for-Duty standards shall be assessed using metrics that are task specific. Sensorimotor performance limits for each metric shall be operationally defined. Countermeasures shall maintain function within performance limits. Post-flight reconditioning shall be monitored and aimed at returning to baseline sensorimotor function*." However, operational performance limits related to mobility (e.g., emergency egress), flight vehicle control (particularly for post-adaptation activities, such as rendezvous/docking and entry/landing), ground vehicle control (e.g., Lunar or Martian rovers), and remote manipulator/teleoperation activities have not yet been established.

The very first astronaut candidates underwent rigorous selection tests, including neurological tests, but NASA conducted little screening for vestibular or sensorimotor problems in subsequent groups of new astronauts, including those in the Space Shuttle program. As evidence evolved from early space programs through the Shuttle missions, sensorimotor and CNS problems began to become prevalent medical findings. Current medical history and exams for astronaut selection include (a) no history of serious ongoing neurological disease, (b) examination by a neurologist, and (c) magnetic resonance imaging of the brain and magnetic resonance angiography of the head.

Abnormalities detected by these methods help to screen out some asymptomatic individuals, some of whom have potentially serious problems. NASA had already required the use of electroencephalography as a part of the selection process before instituting these additional rigorous neurological examinations. Attempts were made historically to use susceptibility to motion sickness, abnormal visual-vestibular function, and postural problems to screen out candidates. Much of this testing, performed by in-house laboratories at the NASA Johnson Space Center, was seldom weighted highly, primarily because researchers in the Neurosciences Laboratories were hesitant to recommend serious limits based on standards that did not reflect operational requirements.

Vestibular precision, or response variability, is an important aspect of interpreting spaceflight sensorimotor results (Diaz-Artiles and Karmali 2021). Understanding individual precision along with accuracy provides a better context to understand adaptative changes and the degree of variability that exists. The high degree of variability across crewmembers in terms of the severity of neurological symptoms, given the current knowledge base, suggests that medical selection and retention standards could be quite effective in minimizing the operational impacts of sensorimotor adaptation. However, the lack of validated assessment tools for predicting sensorimotor adaptation, or an individual's inability to adapt, has hindered the development of relevant selection standards despite the fact that capability for clinical diagnosis of vestibular disorders was greatly advanced during the Space Shuttle era from direct spin-offs of Shuttle projects (e.g., postural testing, eye measurement technology, etc.) (Reschke et al. 2013). Although selection and retention standards for sensorimotor function have remained limited to neurological screenings of reflex functions consistent with standard aviator flight physical examinations, extensive selection standards are now in place for vision, audition, and other sensory functions.

Flight rules have been used to minimize the operational consequences of vestibular and sensorimotor changes associated with microgravity. These rules primarily limited crew activities after G-transitions, particularly during the early days of flight, to allow the crew to adapt to SMS. Examples of rules are prohibition of extravehicular activities until the third day on-orbit because of concerns related to emesis in the spacesuits and restriction of driving or flying until the third day after short-duration flights. When Shuttle flights resumed after the loss of Space Shuttle *Columbia*, computerized dynamic posturography testing was implemented as an aid for the return-to-duty assessment to supplement preflight and post-flight neurological examinations (Wood et al. 2015).

Future standards assessments will need to be both compatible with mass / volume / power constraints of exploration vehicles and multi-disciplinary to have maximum impact. Ultimately, the standards will need to provide thresholds to guide the fitness for duty decision with efficient inflight assessments. These may include unobtrusive monitoring, e.g., head and body movements during natural activities (Nouredanesh et al. 2021). Another approach is to provide short screening assessments like the neurological exams currently utilized (Clark et al. 2019; Sirven et al. 2021). Stone and colleagues have developed a brief multidimensional oculometric screening tool for subtle neurological signs of subclinical neurological insults (Liston and Stone 2014; Liston et al. 2017). This type of screening tool may have the benefit of detecting subtle effects of sleep disruption and other behavioral decrements (Stone et al. 2019; Tyson et al. 2021) which may not be detected by complex tasks that may involve learning (e.g., operational trainers, Wong et al. 2020). Nevertheless, tools used for "just-in-time" training of complex manual control tasks are recommended for assessment of operational readiness, such as those devised to practice the landing task sequence for Shuttle landings (Dempsey and Barshi 2021; Kennedy et al. 1997), rover telerobotics (Pilot-T, Bubeev et al. 2019), and track-and-capture activities (Ivkovic et al. 2019).

2. Risks during Vehicle Egress and Extravehicular Activities

Ensuring that crewmembers are able to egress the vehicle in the event an emergency occurs during the post-landing timeframe is essential to allowing them to survive or avoid serious injury during such an event. The crewmembers should also be able to function in 1-g environment in case of return to Earth, or in a 1/6-g or 3/8-g environment in case of lunar or Mars landing. Factors that affect egress in a timely manner include (a) visually determining hazards outside the vehicle, such as the presence of fire or debris; (b) having a hatch that can be operable by a single crewmember without the use of tools; and (c) having an egress path that allows egress of all occupants in a timely manner. Determining if it is safe to egress the vehicle and having an egress path requires good situational awareness, spatial orientation, and a mental representation of space. Opening the hatch, egressing the vehicle, and walking in enough time to protect from post-landing hazards may be compromised if crewmembers are incapacitated or in a deconditioned state. Orion and other commercial vehicles are currently designed for a parachuted landing on water after long-duration missions. In these water landing scenarios, the interaction between the adapted microgravity sensorimotor state and the prevailing unstable support surface induced by various sea state conditions will increase the risk associated with an emergency egress situation.

During Expedition 6 to the ISS, a series of unplanned events serendipitously created an analog mission for a trip to and landing on Mars. A spacecraft malfunction caused a ballistic entry displacing the landing site about 475 km off course, resulting in an approximately 5-hour delay for arrival of the ground support team. This gave the crew an opportunity to perform spacecraft safing, egress, and to set up survival gear without any outside help (Pettit 2010). The safing involved reading procedures, flipping switches, and pushing buttons on the control panel to power down unneeded equipment so that battery life for radio operations would be extended. Since the Soyuz capsule landed on its side, these operations were done from a position of being strapped into a seat fixed on a slanted ceiling. The crew opened the hatch, unstrapped, and crawled out. Following egress, they deployed the survival gear that was stowed in numerous small bundles throughout the spacecraft. Included were warm woollen clothes, food, water, a medical kit, a portable radio, and a signalling kit.

One crewmember reported that "performing these basic survival tasks was not easy. Moving was provocative. […] Walking was laborious but was done as needed shortly after landing. I had trouble walking but could crawl. […] There were no systemic aches or pains associated with movement. We had good muscle strength. […] My limbs felt heavy because my brain was not yet compensating for their weight. [..] Upon returning, the brain had not yet kicked in this compensation which takes about 10 to 15 hours. Slow and deliberate motions were readily made with sufficient motor control to connect electrical wire harnesses, antennas, cycle switches on control panels, and shoot a shotgun pistol [for flares]. Motor control for operating the spacecraft mechanisms and survival gear was not a problem. However, fast coordinated movement was not possible for me." (Pettit 2010). In addition, this crewmember recommended that "a well-designed [Mars] mission should have minimal demands on the crew after landing, giving them a few days for adaptation before engaging in significant operational tasks."

3. Risks during Piloted Landings and Rendezvous/Docking

Piloting a spacecraft through entry and landing is one of the most difficult tasks associated with spaceflight. The consequences of failing to successfully complete this task could be catastrophic, resulting in loss of life, vehicle, or other assets. While all piloted landings from space have been successful to date, the evidence presented in this report suggests that the landing performance metrics have been outside of desired limits for both the Shuttle and the Lunar Lander. To the (currently unknown) extent physiological adaptations play a role in these performance decrements, we can anticipate that the risk of failure will become much greater during Mars missions. There is strong evidence that the six-month outbound trip (without artificial gravity) will cause a much more profound sensorimotor adaptation to 0 g than occurs during a 2-week Shuttle mission. This will likely cause a more profound physiological response to the G-transition during entry/landing; however, the impact of the reduced amplitude (3/8 g vs. 1 g) of the transition is unknown. Furthermore, piloting recency will decrease from 1-2 weeks during the Shuttle program to approximately six months during a Mars mission, decreasing the probability that a pilot will be able to fly through any spatial disorientation that accompanies the G-transition. Even piloted landings on the Moon present some unique risks, owing to the effects of the novel gravitational environment on spatial and geographic orientation and the potential for lunar dust obscuring vision during critical phases of landing.

Manual control during exploration spaceflight consists of both planned automated supervisory control and unplanned crew override. This crew override capability is critical to enable overall mission success during landing contingencies. During the Space Shuttle Program, crew manual capability was implemented for landing, docking, systems management, reconfiguration of the flight control system, subsystem reconfiguration, Remote Manipulator System (RMS), and payload operations. The Russians provided a manual backup to the primary automatic capability for on-orbit orientation and attitude control, deorbit burn, and docking the Soyuz spacecraft to a space station (Salyut, Mir, and ISS). Based on a thorough review of significant manual control events, it was concluded that at least 35 close calls could have resulted in loss of mission had crew manual control capabilities not been available to support continued mission operations (NASA Flight Safety Office 2013). As described in a recent white paper from the Flight Operations Directorate (FOD, Koerner 2019), "an automated system monitored by crew that has the capability to gracefully transition to a blended auto/manual system, when crew are needed for control, is the safest and the ideal manual control option to accomplish a lunar landing." This FOD white paper reviewed several examples from Apollo 11-17 missions of manual control success, including contingency docking procedures (Apollo 14 and 16), using the lunar module as the controlling vehicle of the docked spacecraft stack in Apollo 13, and takeover using a blended manual/auto control during all six Apollo landings due to hazardous terrain at the automated system's targeted landing site. There was one instance during the Shuttle program (STS-32) in which contingency manual crew control of the orbiter vehicle was used to regain control of the vehicle (NASA Flight Safety Office 2013). Therefore, despite the risks associated with manual control associated with sensorimotor alterations, there is strong evidence for the need for manual control override capabilities during exploration missions.

4. Risks during Rover Operations and Remote Manipulator System Operations

The risk of performance failure (i.e., loss of vehicle control) while driving an automobile is high for those having vestibular deficiencies and for those whom cognitive and/or sensorimotor functions are impaired by ethanol, fatigue, or certain medications (Cohen et al. 2003). Crewmembers readapting to Earth-gravity following return from spaceflight exhibit similar performance decrements, and, as a result, are currently restricted from driving automobiles for a short time (2-4 days) after Shuttle missions and a longer time (8-12 days) after ISS missions. The impact of sensorimotor adaptations on driving rovers on either the Moon or Mars is unknown. While the potential consequences of performance failure while driving a rover are less than those of piloting a space craft through entry and landing, the possibility of crew injury (or death) or loss of the rover exists, particularly in the vicinity of steep-sided craters. The duration of the initial adaptation period to the Lunar or Martian gravity environment is also unknown, and, while likely to be proportional to the time spent in 0-g transit, cannot be determined until it can be measured on the planetary surface. Thus, the amplitude and duration of increased risk during rover driving are currently unknown.

Apart from the Mir/Spektr incident, performance data on rendezvous/docking has so far eluded the authors. However, evidence provided above suggests that the incidence of performance failure during remote manipulator operations aboard the Shuttle and ISS has been fairly well characterized (at least operationally). There is no reason to suspect that performance of these 0-g operations will be any different from our ISS experience during an outbound transit to Mars. Thus, we would not expect the risk to increase. However, the risk impacts of an additional 18 months at Mars gravity followed by six months at 0 g during return transit are unknown and may well lead to an unacceptable range.

The risk of performance failure during operation of any complex system is multi-factorial. However, operation of any system requiring good visual acuity, eye-hand coordination, balance/locomotor skills for surface operations, spatial orientation, and/or cognition could be impaired by physiological adaptations to novel gravitational environments. The risk of impairment is generally greatest during and soon after G-transitions, but the amplitude and duration of the increased risk would need to be evaluated on a system-by-system basis.

5. Risks during Near-Term Missions

The current sensorimotor risk is now high in priority given the prospect of long-duration Mars missions, planned water landings following long-duration ISS and exploration missions, and the requirement for manual control override during lunar landings. There is significant evidence showing sensorimotor alteration after as little as a few weeks of exposure to spaceflight environments, and that severity increases with increasing exposure time. While these issues may be more severe for Mars missions without artificial gravity, significant risks remain quite real even for more standard ISS and Lunar operations. As the Columbia Accident Investigation Board report warned us repeatedly, a small number of successes without catastrophic failure (e.g., a little over 100 Shuttle landings and 6 lunar landings) does not mean that risk, including human sensorimotor adaptation risks, can be ignored. The near misses reported above provide evidence in this regard. Given the reentry profiles and cross-coupled Coriolis effects induced by the drogue parachutes under nominal Orion re-entry/descent/landing scenarios, it will likely be a much more difficult sensorimotor environment than for Shuttle landings. Finally, the proper resolution of automation-human control authority decisions requires an objective and quantitative understanding of sensorimotor compromises. The risk of sub-optimal decisions in this regard has important ramifications for overall mission safety/reliability calculations. Thus, we recommend that this risk be considered high priority for all spaceflight mission scenarios.

The risks associated with long-term health are unknown and require additional characterization. While the contribution of age-related vestibular impairment to balance impairment in the astronaut cohort is not high operational priority, similar research gaps regarding age-related vestibular loss are currently being pursued by the National Institutes of Health (Agrawal et al. 2020) and provide a framework for understanding the interaction of spaceflight and aging. While most of the sensorimotor effects are considered adaptive in nature, recent concerns over long-term adverse effects on the brain (Hupfeld et al. 2021b) have resulted in additional priority for longer term follow-up. Longer term monitoring and treatment are addressed in NASA's Transition Authorization Act of 2017 referred to as the "TREAT Act." The TREAT Act authorizes NASA to monitor, diagnose, and treat medical and psychological conditions associated with spaceflight.

The following table provides the current sensorimotor risk ratings (likelihood x consequence, or LxC) for the various Design Reference Missions and for long term health.

Risk Ratings and Dispositions per Design Reference Mission (DRM) Category

DRM Categories	Mission Type and Duration	Operations		Long-Term Health	
		LxC	Risk Disposition *	LxC	Risk Disposition *
Low Earth Orbit	Short (<30 days)	1x2	Accepted	1x2	Requires Characterization
	Long (30 days-1 year)	1x2	Accepted	2x2	Requires Characterization
Lunar Orbital	Short (<30 days)	1x2	Accepted with Monitoring	1x2	Requires Characterization
	Long (30 days-1 year)	1x2	Accepted with Monitoring	2x2	Requires Characterization
Lunar Orbital + Surface	Short (<30 days)	3x5	Requires Mitigation/Standards Refinement	1x2	Requires Characterization
	Long (30 days-1 year)	3x5	Requires Mitigation/Standards Refinement	2x2	Requires Characterization
Mars	Preparatory (<1 year)	1x2	Accepted with Monitoring	1x2	Requires Characterization
	Mars Planetary (730-1224 days)	4x2	Requires Mitigation/Standards Refinement	2x2	Requires Characterization

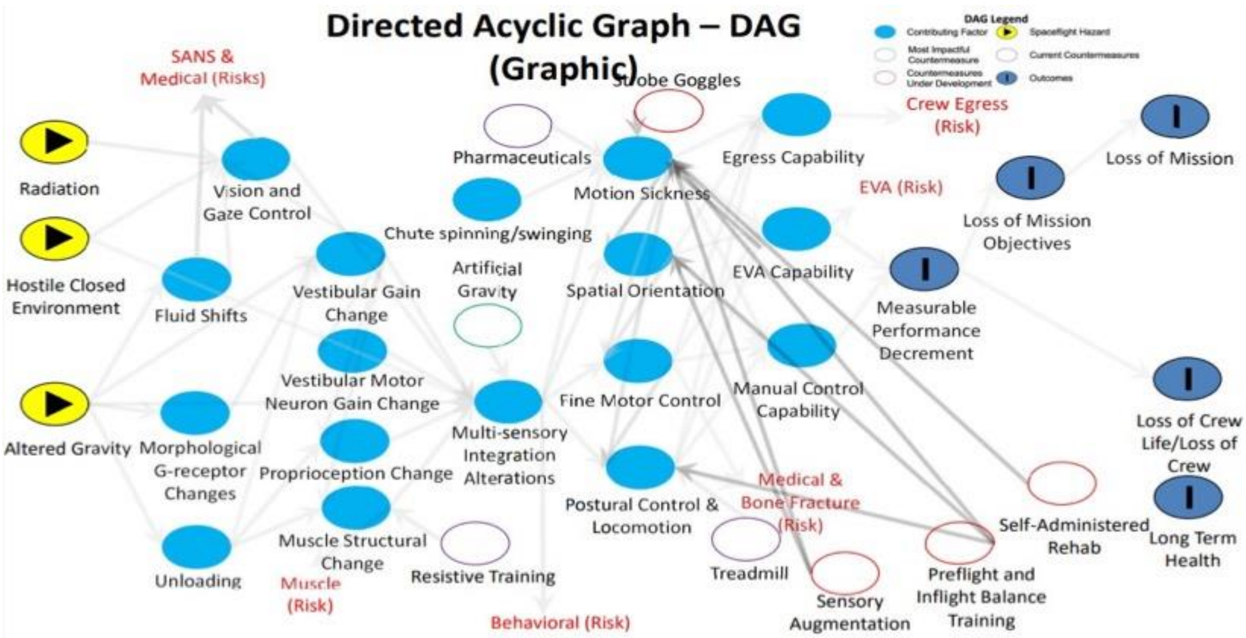
Note: LxC is the likelihood and consequence rating. The information above was last approved by the Human System Risk Board in 12/2020.

Table 2. LxC Sensorimotor Risk Ratings for DRMs and Long-Term Health

VII. DAG REVIEW AND INTEGRATION WITH OTHER RISKS

A. DAG Review

This section reviews the currently accepted Directed Acyclic Graph (DAG) and Level of Evidence assessment of each arrow (relationships), as supported by evidence presented in the report. Changes to this section should be done shortly after DAG updates are provided (this requires coordination with HSRB).



Approved by HSRB December 10, 2020

Figure 13. Latest Sensorimotor Risk DAG

Sensorimotor DAG Narrative

The Sensorimotor Risk is primarily derived from **Altered Gravity** environmental changes but also has effects from **Radiation** and **Hostile Closed Environment**.

Time spent in an **Altered Gravity** environment causes physical changes to the body, including:

- **Fluid Shifts** – fluid shifts from the lower body towards the upper body.
- **Musculoskeletal Unloading** – end-organ changes (e.g., otoconia size, changes in neural synapses) to physical unloading.
- **Morphological G-Receptor Changes** – cellular responses to physical unloading.

These changes lead to physiologic changes that affect:

- **Vision and Gaze Control** – vision is the ability to see and gaze control is the ability to orient the eyes and maintain fixation on a desired visual target. **Radiation** can induce cataracts that affect vision.

- **Vestibular Gain Changes** – the relationship between accelerations, including gravitational and vestibular responses.
- **Vestibular Motor Neuron Changes** – vestibular neurons adapt to reduced or increased firing rates and become more or less sensitive. **Radiation** and the **Hostile Closed Environment** are suspected to affect motor neurons.
- **Proprioception** – a global term that encapsulates multiple internal sensors that monitor the relationship between one body segment and another.
- **Muscle Structural Changes** – reduced loading on muscle, tendons, and ligaments that cause both structural and functional changes in strength.

All of these physiologic changes send signals that must be interpreted by the brain (here represented by **Multi-Sensory Integration Alterations,)**. **Radiation** and the **Hostile Closed Environment** produce effects on the central nervous system suspected to impact this central processing.

The central nervous system must integrate information from all of these systems. **Multi-Sensory Integration Alterations** lead to functional impairments such as:

- **Motion Sickness** – occurs when vestibular and ocular signals from the brain are conflicting.
- **Fine Motor Control** – limits the ability to perform tasks that require delicate control.
- **Postural Control and Locomotion** – refers to the balance and ability to walk that are required to perform physical tasks in a gravity environment.

The severity of these functional impairments directly impacts **Individual Readiness** and **Crew Capability** and specific tasks, including:

- **Manual Control of Vehicles** – which depends on **Fine Motor Control** and perception.
- **EVA (Risk)** – through the increased likelihood of falls or injury.
- **Crew Egress (Risk)** – through the increased likelihood of falls or injury.

Distance from Earth affects the mass, power, volume, and bandwidth allocations for **Vehicle Design** the **Crew Health and Performance System** in particular. These include:

- **Exercise** such as **Treadmill Exercise** which affects **Postural Control and Locomotion**.
- **Medical Prevention Capabilities** such as the following and are still experimental:
  - **Strobe Goggles**
  - **Self-Administered Rehab**
  - **Sensory Augmentation**
  - **Balance Training**
- **Medical Treatment Capabilities** – which include medications such as Phenergan, etc. that are susceptible to stability issues listed in the **Pharm (Risk)**.
- **Artificial Gravity** as a countermeasure, which holds the potential to significantly reduce the Sensorimotor Risk but is high cost to implement.

B. Integration with other risks

As described in the DAG narrative above, the Sensorimotor Risk is primarily integrated across the following HSRB risks:

- Risk of Reduced Physical Performance Capabilities Due to Reduced Aerobic Capacity (Aerobic Risk)
- Risk of Adverse Cognitive or Behavioral Conditions and Psychiatric Disorders (Behavioral Med. Risk)
- Risk of Bone Fracture due to Spaceflight-induced Changes to Bone (Bone Fracture Risk)
- Risk of Orthostatic Intolerance During Re-Exposure to Gravity (OI Risk)
- Risk of Cardiovascular Adaptations Contributing to Adverse Mission Performance and Health Outcomes (Cardiovascular Risk)
- Risk to Vehicle Crew Egress Capability and Task Performance as Applied to Earth and Extraterrestrial Landings (Crew Egress Risk)
- Risk of Injury from Dynamic Loads (Dynamic Loads Risk)
- Risk of Injury and Compromised Performance Due to EVA Operations (EVA Risk)
- Risk of Performance Decrement and Crew Illness Due to Inadequate Food and Nutrition (Food and Nutrition Risk)
- Risk of Hearing Loss and Performance Decrements Due to Acoustics Issues in Space (Hearing Loss Risk)
- Risk of Adverse Outcomes Due to Inadequate Human Systems Integration Architecture (HSIA Risk)
- Risk of Adverse Health Outcomes & Decrements in Performance due to inflight Medical Conditions (Medical Conditions Risk)
- Risk of Impaired Performance Due to Reduced Muscle Size, Strength, and Endurance (Muscle Risk)
- Risk of Adverse Health Outcomes and Performance Decrements resulting from Non-Ionizing Radiation during Spaceflight (Non-Ionizing Radiation Risk)
- Risk of Ineffective or Toxic Medications During Long-Duration Exploration Spaceflight (Pharm Risk)
- Risk of Spaceflight Associated Neuro-ocular Syndrome (SANS Risk)
- Risk of Performance Decrements and Adverse Health Outcomes Resulting from Sleep Loss, Circadian Desynchronization, and Work Overload (Sleep Risk)

VIII. KNOWLEDGE BASE

A. Gaps in knowledge

The Human Health Countermeasures (HHC) Element, representing the sensorimotor (SM) discipline, have identified the series of knowledge and mitigation gaps listed below. Each of them must be filled before this risk can be fully assessed and/or mitigated.

SM-101: Characterize the effects of short and long-duration weightlessness, with and without deep-space radiation, on postural control and locomotion (gross motor control) after G transitions.

SM-102: Characterize the effects of short and long-duration weightlessness, with and without deep-space radiation, on manual control (fine motor control) after G transitions.

SM-103: Characterize the effects of short and long-duration weightlessness, with and without deep-space radiation, on spatial orientation and motion sickness after G transitions.

SM-104: Evaluate how weightlessness-induced changes in sensorimotor/vestibular function relate to and/or interact with changes in other brain functions (sleep, cognition, attention).

SM-201: Develop and test postural control and locomotion countermeasures, including human factors aids.

SM-202: Develop and test manual control countermeasures, such as vibrotactile assistance vest, and other human factors aids.

SM-203: Develop and test SMS countermeasures.

SM-204: Develop and test post-planetary-landing self-administered testing and rehab tool.

SM-301: Test the finalized combined CM Suite in flight.

B. State of Knowledge/Future work

The mitigation strategy involves prevention, monitoring, and mitigation (treatment) of sensorimotor and neuro-vestibular disturbances induced by spaceflight that affect critical mission tasks. Operational countermeasures are being developed to address balance and locomotor deficits as well as motion sickness post-flight. This includes preflight and inflight training exercises, post-flight rehabilitation, sensory augmentation, and combining non-pharmacological countermeasures with new anti-motion sickness drug formulations. Future plans also include defining standards that are tied to fitness for duty for exploration tasks and providing a quantitative index of readiness to perform key exploration tasks, as well as validating self-administered integrative countermeasure approaches suitable for autonomous exploration missions. Studies will also address the risk associated with manual override of a lunar landing by characterizing post-flight performance on a lunar landing motion-based simulation and testing countermeasures, such as enhanced displays or just-in-time training, on similar motion-based simulations. Finally, theHHC Element is also working with the Human Factors and Behavioral Health (HFBP) Element and the Space Radiation (SR) Element in support of the Integrated CBS (CNS/BMed/Sensorimotor) plan.

IX. CONCLUSION

A large body of sensorimotor research data obtained from spaceflight experiments over the past half-century demonstrates significant decrements in oculomotor control, eye-hand coordination, spatial orientation, posture\locomotor control and cognition during spaceflight missions. These changes are most severe during and after G-transitions, the most crucial time for many critical operational tasks (e.g., landing and egress). Unfortunately, only limited information is available to assess the operational impacts of these changes. Some of the operational observations are compelling but are confounded by unknown environmental and engineering influences. Others appear to raise little concern, but the safety margins are difficult to estimate. During exploration missions, we can expect that most performance circa G-transitions will be degraded further by the influence of extended time in flight (Mars missions), but the potential influence of extended time in hypogravity (Mars and Lunar missions) is unknown.

The true operational risks associated with the impacts of adaptive sensorimotor (and other) changes on crew mobility and abilities to control vehicles and other complex systems will only be estimable after the gaps (identified above) have been filled and we have been able to accurately assess integrated performance in off-nominal operational settings. While exclusive crew selection procedures, intensive crew training, and highly reliable hardware/software systems have likely minimized the operational impacts of these sensorimotor changes to date, the impacts of new mission and vehicle designs may offset some of benefits.

Forward work in this area must account for the multi-factorial nature of the problem. While sensorimotor and behavioral (cognitive) disciplines clearly have roles to play, muscle (strength and endurance) and cardiovascular (orthostatic tolerance) disciplines also must be involved, as should human factors experts, training experts, vehicle designers, mission designers, and crewmembers. Mechanisms for facilitating cross-disciplinary investigations are only beginning to be established. Future success will clearly require more progress in these approaches.

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XI. TEAM

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XII. LIST OF ACRONYMS

AFT	Autogenic Feedback System
ARED	Advanced Resistive Exercise Device
AURL	Aquarius Undersea Research Laboratory
CDP	Computerized Dynamic Posturography
CEVIS	Cycle Ergometer with Vibration Isolation System
CNS	Central Nervous System
COLBERT	Combined Operational Load Bearing External Resistance Treadmill
DAG	Directed Acyclic Graph
DOME	Device for Orientation and Motion Environments
DRM	Design Reference Missions
DVA	Dynamic Visual Acuity
EVA	Extra-Vehicular Activity
FMT	Functional Mobility Test
FTT	Functional Task Test
GVS	Galvanic Vestibular Stimulation
HDBR	Head Down Bed Rest
HUD	Head Up Display
HRP	Human Research Program
IBMP	Russian Institute of Biomedical Problems
IM	Intramuscular

iRED	interim Resistive Exercise Device
ISS	International Space Station
LBNP	Low Body Negative Pressure
LCD	Liquid Crystal Display
LM	Lunar Module
LxC	Likelihood by Consequence Risk Rating
MESA	Apollo Modularized Equipment Stowage Assembly
MRI	Magnetic Resonance Imaging
NEEMO	NASA's Extreme Environment Mission Operations
NPSA	Neck Pneumatic Shock Absorber
OCR	Ocular Counter Rolling
OKN	Optokinetic Nystagmus
OTTR	Otolith Tilt-Translation Reinterpretation
OVAR	Off Vertical Axis Rotation
PAT	Preflight Adaptation Training
PFMS	Post-Flight Motion Sickness
PSOI	Post Spaceflight Orthostatic Intolerance
ROTTR	Rotation Otolith Tilt-Translation Reinterpretation
SA	Sensorimotor Adaptability
SANS	Spaceflight Associated Neuro-ocular Syndrome
SD	Spatial Disorientation
SMS	Space Motion Sickness
SR	Stochastic Resonance
STA	Shuttle Training Aircraft
STS	Space Transportation System (Space Shuttle)
TCC	Time to Complete the Course
TSAS	Tactile Spatial Awareness System
TTD	Tilt-Translation Device
TVIS	Treadmill Vibration Isolation System
V2Suit	Variable Vector Countermeasure Suit
VEMP	Vestibular Evoked Myogenic Potentials
VIIP	Vision Impairment and Intercranial Pressure
VOR	Vestibulo-Ocular Reflex
VRI	Visual Reorientation Illusion
VRT	Vestibular Rehabilitation Therapy
WHIP	Wheelchair head Immobilization Paradigm

XIII. APPENDIX A: SENSORIMOTOR GUIDELINES WHITEPAPER

The following is an excerpt from a Sensorimotor Guidelines Whitepaper to provide a framework for guidelines to accommodate the needs of the crew and effectively leverage the human capabilities to ensure mission success during planned lunar design reference missions.

A. Physiological countermeasure and conditioning guidelines

Outside of pharmaceuticals to suppress motion sickness and vertigo, countermeasures that can mitigate vestibular and sensorimotor alterations remain very limited. Countermeasure approaches for sensorimotor conditioning have been targeted for different phases of spaceflight missions. These include preflight training to facilitate transitions between gravitoinertial levels, inflight exercise to minimize deconditioning while in microgravity, incrementally increasing movements following G-transitions, and post-landing exercises to enhance adaptation.

Preflight training

1. Motion sickness: Due to the lack of an appropriate analog and ability to predict susceptibility from terrestrial motion stressors, there is currently no recommended preflight desensitization training to decrease inflight or reentry motion sickness. Instead, training on strategic approaches on how to recognize and manage early symptoms is recommended, e.g., recognizing lags in symptom progression. This includes limiting provocative head and body movements during early phases and, when symptomatic, using feet and body restraints to maintain contact cues while remaining aligned with familiar visual “upright” spatial references. Crewmembers should be trained on optimal timing of medication, e.g. prevention versus rescue treatment, and the importance of fluid, electrolyte, and glucose replacement.
2. Sensorimotor and spatial disorientation training: Exposure to multiple sensory challenges enhances the ability of the nervous system to adapt to a novel environment or task, i.e., facilitates “learning to learn” (Bloomberg et al. 2015b). Variations in practice have been employed as a training paradigm for generalizing motor skills (Mulavara et al. 2009). Preflight spatial disorientation training may include virtual reality training to simulate spatial disorientation and navigation problems inside spacecraft (Aoki et al. 2007) or use of galvanic vestibular stimulation (MacDougall et al. 2006; Moore et al. 2006) to learn to strategically ignore disorienting vestibular cues.
3. Astronaut Strength, Conditioning and Rehabilitation Specialist (ASCR) preflight training goals to prepare for flight include muscle conditioning (strength, endurance, flexibility, power, coordination and stamina), metabolic fitness, and work on individual areas of concern (program balance). Preflight training includes familiarization with in-flight exercise operation and encouraging proper technique with emphasis on injury prevention.

Inflight training

1. Physical exercise constitutes a critical component of the muscle, aerobic, and bone countermeasure program for long duration flights (Kozlovskaya 2002). ASCR goals are to protect functionality and capability and minimize losses in strength, endurance,

flexibility, power, coordination, stamina, metabolic fitness, and bone. The planned progression of loads and speeds to maximize conditioning is based on preflight fitness levels, exploration exercise hardware capabilities, and periodic inflight fitness evaluations.
2. There is no current countermeasure for lack of otolith gravitational loading. Inflight sensorimotor training should focus on maintaining proprioceptive function that will be useful compensating for altered gravitational cues during subsequent G-transitions.

Training for reentry and post-landing

1. The strategy is to minimize provocative head movements and to systematically increase the amplitude of movements to promote readaptation while limiting motion sickness. Prophylactic motion sickness medications, proper hydration (fluid loading), and sleep management prior to re-entry will improve capacity.
2. During reentry, most head movements that change orientation relative to G-vector can be provocative. Temporarily holding the head still and closing eyes if experiencing vertigo may help reduce symptoms or prevent symptom progression. Crewmembers should be trained to strategically limit head movements in pitch and roll at first and only slowly incrementally increase the amplitude of head movements so as to not provoke motion sickness symptoms. The key is to maintain the amplitude and rate of head movements within the range tolerated by the individual.
3. Immediately following landing, the earlier introduction of head movements and other motor activity, as long as they are self-paced and within one's threshold for motion tolerance, is recommended to facilitate adaptation. As symptoms allow, head and body movements can be progressively increased to promote adaptation. Crewmembers should plan to take frequent rests with head still and eyes closed to limit symptom progression. This may require reclining or laying down to minimize orthostatic symptoms (lowered blood pressure and fainting).
4. For water landings on return to Earth: Crews should be trained to avoid aspiration of vomitus with inverted capsular orientations (e.g., loosen restraints, raise helmet visor, turn head sideways).
5. Reconditioning on lunar surface or following return to Earth: The more mobile a crewmember is following landing the quicker the sensorimotor symptoms will be resolved (similar to the vestibular rehabilitation motto "when you move, you improve"). Every crewmember returns with a different level of functionality and progresses at different rates. As simple movements become less provocative, more complex movements can be introduced to continually challenge the limits of an individual's motion tolerance threshold (Wood et al. 2011).

Planning for EVAs

1. Individual health assessments are recommended to account for variability in motion sickness symptom severity and task readiness.
   a. Given the potential for quick progression from nausea to emesis, EVAs should be delayed for crewmembers with moderate to severe motion sickness symptoms or persistent illusions or sensitivity to head movements.

b. EVAs for crewmembers with mild motion sickness symptoms or intermittent illusions should be limited in duration and difficulty, avoiding provocative movements or challenging terrain that may contribute to fall risk.
c. It is recommended that balance and mobility tasks be included in the health assessments for EVAs that have increased complexity.

Manual control considerations

1. Pre-flight training is required for Rendezvous Proximity Operations Docking and Undocking (RPODU), Lunar Descent/Ascent and Landing. An In-Flight Trainer (IFT) of a high fidelity is recommended to train the crew to organize and process visual, aural, vestibular, and proprioceptive cues and to produce an appropriate motor response. Motion based simulations provide a secondary platform for protocol evaluation and training of complex tasks requiring multi-crewmember coordination of manual crew override.
2. Just-in-time (JIT) on-orbit training using a laptop-based trainer (as well as virtual reality and haptic devices) is recommended to practice the landing task sequence to maintain task proficiency, similar to the Shuttle Pilot (Dempsey and Barshi 2021; Kennedy et al. 1997), Canadarm2 track-and-capture activities (Ivkovic et al. 2019), and landing / telerobotic controls by the Russian space agency (e.g., Pilot-T experiment, Bubeev et al. 2019).
3. It is recommended the JIT on-orbit trainer be designed to provide task proficiency metrics to be used as a fitness for duty assessment prior to initiating RPODU, or descent/ascent activities.

B. Engineering design considerations

Engineering solutions should be designed for different mission phases to enable success given the sensorimotor decrements reviewed above. Two sets of critical activities potentially affected by G-transitions should be considered: capsule egress and early EVA and manual control.

Capsule egress and early EVA considerations

1. We recommend that handholds and aids are in place to allow the crewmember the ability to sit (or preferably lay) quickly down with onset of symptoms.
2. Handholds or restraints when standing should be available to stabilize body motion.
3. The fall risk will be greatest with the initial EVAs. Therefore, deployment of the egress aids (e.g., ladders, platforms) need to be designed with appropriate handrails and/or fall protection.
4. Deployment of equipment (e.g., rafts during water landings, egress aids during lunar landings) should be designed to minimize large head movements (e.g., looking overhead) or lifting with both hands (prefer to maintain one hand on fixed structure for stability).
5. Mobility aids during EVAs should be available to minimize bending over maneuvers (grappling poles) or to aid during recovery from fall.

Manual control considerations

1. The introduction of manual override capabilities must be implemented to enable crews to takeover control while minimizing human error. With manual control comes a need to give the crew adequate situational awareness and insight to monitor the automated system and, if needed, to transition to manual control (Koerner 2019).
2. Given the variability in crew decrements, redundancy should be designed in displays and controls to allow critical tasks and contingency operations to be performed by multiple crew positions.
3. Time critical controls should be easily accessible to minimize large provocative movements. Display and control switch design should account for decreased dynamic visual acuity, as well as decreased accuracy in pointing and eye hand coordination.
4. Handholds are recommended around control panels (e.g., touch screen) to improve accuracy in pointing with sufficient controls or inhibits in place to preclude inadvertent engagement of manual override capabilities.
5. It is recommended that manual crew override involves switching from automatic to a blended manual mode using the minimum degrees of freedom necessary to perform functions critical for crew safety or primary mission objective (e.g., landing aim-point redesignation).
6. Sufficient time must be provided for the crewmember to get a feel for the vehicle handling characteristics prior to final approach and landing/docking.
7. The FOD whitepaper addressing manual control also provided the rationale for windows. Window views provide situational awareness and confirming cues to the crew that the vehicle is performing as expected (Koerner 2019). Providing surface-fixed visual reference through windows will also help resolve ambiguous sensory cues.
8. Once transitioning to manual control, the vehicle handling qualities must enable the crew to achieve the desired results. The recommended guidelines for satisfactory handling qualities has already been addressed in a separate white paper (Handling Qualities Task Team 2020).

C. Procedural control considerations

Procedural controls include logistics, planning, and operational support that can be provided to minimize crew health risk. During exploration missions, the emphasis shifts toward more autonomy and providing the tools for crewmembers to self-administer rehabilitation countermeasures and conduct health assessments.

Capsule egress and early EVA considerations

1. Based on the evidence reviewed above, one can expect a large range of responses. Increased duration in microgravity will increase the incidence of symptoms and the time required for recovery.
2. Development of pre-worked, prioritized content and timelines for EVA is recommended, with the ability to change roles depending on crew readiness (see assessment above).
3. Early EVAs should minimize provocative motions (e.g., bending down for sample collection), be of shorter duration, and avoid challenging terrain. Readiness may depend on the complexity in deploying egress aids (e.g., ladders) during the initial EVAs.

4. "Transfer" EVAs into surface assets may be performed at low risk but may require mobility aids to facilitate transfer.
5. Planned rests following EVAs are recommended to allow for recovery.

Manual control considerations

1. Plan for increased refresher training to be performed on board prior to critical operations.
2. Plan for distributed workload among crew during critical mission phases to minimize task overload.
3. Plan for redundancy in monitoring displays and window views for spatial and temporal awareness during RPOD approach and lunar landings.